Impact of gene patents and licensing practices on access to genetic testing for long QT syndrome

Misha Angrist, PhD, Subhashini Chandrasekharan, PhD, Christopher Heaney, BA, and Robert Cook-Deegan, MD

Abstract: Genetic testing for long QT syndrome exemplifies patenting and exclusive licensing with different outcomes at different times. Exclusive licensing from the University of Utah changed the business model from sole provider to two US providers of long QT syndrome testing. Long QT syndrome is associated with mutations in many genes, 12 of which are now tested by two competing firms in the United States, PGxHealth and GeneDx. Until 2009, PGxHealth was the sole provider, based largely on exclusive rights to patents from the University of Utah and elsewhere. University of Utah patents were initially licensed to DNA Sciences, whose patent rights were acquired by Genaissance, and then by Clinical Data, Inc., which owns PGxHealth. In 2002, DNA Sciences, Inc., "cleared the market" by sending cease-and-desist patent enforcement letters to university and reference laboratories offering long QT syndrome genetic testing. There was no test on the market for a 1- to 2-year period. From 2005–2008, most long QT syndrome-related patents were controlled by Clinical Data, Inc., and its subsidiary PGxHealth. Bio-Reference Laboratories, Inc., secured countervailing exclusive patent rights starting in 2006, also from the University of Utah, and broke the PGxHealth monopoly in early 2009, creating a duopoly for genetic testing in the United States and expanding the number of genes for which commercial testing is available from 5 to 12. ***Genet Med* 2010:12(4):S111–S154.**

Key Words: *patents, intellectual property, long QT syndrome, arrhythmia, University of Utah, genetic testing*

EXECUTIVE SUMMARY

- Familial long QT syndrome (LQTS) affects 1 in 3000 newborns. It is a Mendelian condition in which patients' hearts do not recharge appropriately after heartbeats and can lead to life-threatening arrhythmias. It accounts for a small but significant fraction of sudden death in young people. Beta-blocker drugs and implantable cardioverter defibrillators are the most common therapies. Patients and those close to them can also endeavor to avoid triggers for arrhythmias such as loud noises or physical or emotional stress.
- Mutations in 12 susceptibility genes account for some 75% of familial LQTS; of that 75%, mutations in three genes account for most cases. Genetic testing for LQTS is important because knowing which gene (and which part of that gene) is mutated can have a direct bearing on decisions regarding preventive measures and pharmacological therapies.
- The major LQTS susceptibility genes were discovered at the University of Utah in the mid-1990s. Their discovery was funded in part by the National Institutes of Health. The first LQTS gene patent was awarded in 1997.
- The University of Utah Research Foundation began licensing patents on LQTS susceptibility genes in the late 1990s. Until recently, at any one time, there was never more than a single licensee of the major intellectual property (IP) attached to the three genes that predispose to the majority of familial LQTS. In 2008, Bio-Reference Laboratories (BRLI) obtained an exclusive license for one of those patents and also for two others, giving it rights to test for LQT3, which accounts for ~10–15% of inherited LQTS. BRLI has since aggregated IP related to susceptibility genes for other forms of LQTS. As a consequence, the patent landscape for LQTS testing has become fragmented between 2 different exclusive licensees.
- In 2002, before a commercial test of five genes was launched under the name FAMILION®, there were at least two other fee-for-service providers of genetic testing; however, they focused their sequencing on regions previously associated with mutations causing LQTS, which amounted to a minority of the five genes' combined coding sequence. Subsequent enforcement of the gene patents prompted at least one diagnostic provider, GeneDx (subsequently acquired by BRLI), to cease testing in 2002. We suggest that, based on incomplete evidence, this probably had a small but tangible negative effect on patient access to genetic testing for LQTS between 2002 and 2004. We believe this negative effect would likely have been larger had there been greater awareness, understanding, and acceptance of genetic testing on the part of cardiologists and electrophysiologists at that time.
- From 2005–2008, most LQTS gene IP relevant to clinical genetic testing was controlled by Clinical Data, Inc., and its subsidiary, PGxHealth LLC. During that period, the company did not sublicense its test to any other diagnostic services in the United States, although it has granted international licenses in Australia, New Zealand, and Europe. It has also granted a research license to a company in Utah.
- In general, clinicians whom we spoke to say that PGxHealth does a very good job of performing genetic testing of the five genes that account for ~75% of LQTS. Its turnaround time for a complex, sequence-based test is typically less than 2 months versus what is often a year or more for research-based testing. The company reports that

From the Center for Public Genomics, Center for Genome Ethics, Law and Policy, Institute for Genome Sciences and Policy, Duke University, Durham, North Carolina.

Robert Cook-Deegan, MD, Center for Genome Ethics, Law and Policy, Institute for Genome Sciences and Policy, Duke University, Box 90141, Durham, NC 27708. E-mail: gelp@duke.edu.

Disclosure: The authors declare no conflict of interest. See Acknowledgments for details.

DOI: 10.1097/GIM.0b013e3181d68293

its turnaround time has been substantially reduced since it began offering the test. PGxHealth's FAMILION testing continues to be widely adopted by cardiologists and electrophysiologists, which the company attributes to its efforts to educate physicians and patients, its customer service, and diligent advocacy for reimbursement policies and payment agreement with insurers and health plans. It can be argued that (and has been by PGxHealth parent Clinical Data) an exclusive license has contributed to the company's skill at performing the test and allowed it to leverage economies of scale. GeneDx parent company BRLI attributes these improvements to the march of technology and the threat of competition.

- PGxHealth has been criticized for occasional laboratory errors (missed mutations and misinterpretations). It is not clear that the laboratory's error rate is outside acceptable norms, or worse than its stated analytical accuracy of >99%. PGxHealth says it implements process changes to ensure that any errors are not repeated, thus leading to improved accuracy over time. Misinterpretation, the company says, can be a subjective phenomenon in a complex disease such as LQTS. PGxHealth consults with experts in the field to review variants of questionable interpretation. It also issues amended reports when interpretations change because of new knowledge in the field.
- PGxHealth performs proficiency testing in conjunction with Michael Ackerman, a researcher and physician at the Mayo Clinic who has the sequencing facilities and diverse genetic samples and clinical profiles necessary to conduct such a program in accordance with the relatively nonspecific regulations set forth by the CLIA, the pertinent federal statute. By all accounts, Dr. Ackerman is an outstanding clinician and researcher who has greatly advanced the cause and treatment of LQTS patients. His financial arrangements with Clinical Data and PGxHealth have been reported to and vetted by Mayo, and his service as a consultant to PGxHealth has been disclosed in publications.
- In 2005, PGxHealth reported allelic dropout in research laboratory screening of LQTS patients. This phenomenon, a technical issue associated with DNA amplification assays, can result in false negatives (i.e., results that report no relevant mutation when in fact a deletion or genomic rearrangement has altered the relevant protein). The company's identification and publication of this problem ultimately increased the sensitivity of LQTS genetic testing.
- The overall yield of FAMILION testing, as reported by PGxHealth in 2007, was 38% vs. 50% for the 1995–2004 era of research-based testing. This lower figure is likely because of an increase in surveillance of borderline cases resulting from the availability of large-scale commercial testing. Another possible factor reducing yield might have been surveillance of fewer genes in the commercial test than in research laboratories prior to 2009.
- PGxHealth has been criticized by at least one clinician (Wendy Chung, who consults for competitor BRLI) for its difficulty in processing paraffin-embedded samples from deceased individuals. Routine extraction of DNA from such samples remains a challenge. Based on the anecdotal accounts that we have received from the company, referring physicians, and potential competitors, we have no evidence that PGxHealth is less (or more) adept at performing this procedure than other commercial diagnostic laboratories.
- Until 2009, PGxHealth tested just five genes in its LQTS testing panel, citing both minimal benefit in light of the rarity of mutations in the 7 other genes known to predispose to LQTS and uncertain clinical interpretation of uncharacterized background variants in these genes. When GeneDx secured exclusive rights on LQTS genes and entered the market, PGxHealth also expanded its testing to more than ten genes.
- Patients who were not found to have a mutation in the genes included in the panel were referred to research laboratories for additional testing. Research laboratories, however, may take months or years to return results. Although it is possible that sublicensing of the right to test the major genes would have made other providers more willing to assume the burden of testing the rarer loci, we cannot know this.
- The recent acquisition of selected LQTS gene patent licenses by BRLI may offer a real-world test of how prices respond to competition and of whether testing technology changes with competition, although the nature of the competition may not be head-to-head for the same mutations unless a cross-licensing arrangement is struck between the rival testing services.
- Newer technologies minimize the cost of adding new mutations, but without competition, the commercial incentive to find new platforms is reduced.
- PGxHealth does not offer prenatal genetic diagnosis for LQTS, effectively making it unavailable in the United States prior to 2009. The company does not have an official policy governing prenatal diagnosis. It claims that there are technical difficulties in distinguishing maternal from fetal DNA; however, other clinicians and would-be LQTS genetic test providers argue that this technical issue is trivial. At least one other former competitor has claimed that the company denied its request to offer prenatal testing. Given the treatable nature of LQTS and the highly variable phenotype, it is not clear how strong the demand would be for prenatal or preimplantation testing. We do know that at least one provider offered prenatal diagnosis in 2002 before patent enforcement actions. GeneDx told us that it does not routinely offer prenatal diagnosis for LQTS but would consider it.
- From 2004–2008, there were three publications in peer reviewed journals that feature PGxHealth scientists as coauthors; most data have been presented at various cardiology meetings. Given the availability of a European mutation database and an international registry containing thousands of LQTS genotypes and phenotypes, PGxHealth's decision not to publish its mutation data prior to 2009 seems unlikely to have harmed patient care. Moreover, PGxHealth does not necessarily have access to the detailed phenotypic data that make mutation catalogs useful. However, one former provider and would-be competitor insisted to us that a knowledge base of certain detailed, clinically useful phenotypic information is likely to come only from high-volume commercial diagnostic laboratories and not from research laboratories. In November 2008, PGxHealth announced that, in collaboration with other researchers at multiple institutions, it would make its LQTS mutation database public in 2009.
- The 5-gene version of FAMILION LQTS testing costs $5400 per index case (a full-sequence test to look for

mutations) and $900 per confirmatory test in additional family members (for identified mutations). For index cases, this breaks down to $74 per amplicon, nearly twice the $38-per-amplicon cost of hereditary breast cancer testing (albeit at a much lower volume), but significantly less expensive than the $129-per-amplicon partial test that was offered in 2002 and the per-amplicon price of some other tests (see case studies on hearing loss and Tay-Sachs/Canavan). Such a cost comparison does not take into account the more cost-effective technologies that have become available in recent years. Several independent cardiologists, researchers, patient advocates, and patients with whom we communicated complained about the cost of the FAMILION test. The cost will also be compared with the precipitous drop in the cost of full genomic sequencing in the foreseeable future. These complaints may have resulted in part from historically incomplete coverage by many payers. To date, the FAMILION LQTS test has received positive coverage decisions from numerous health plans. The company has also established simplified billing codes. Among government payers with favorable coverage policies are TRICARE and Medicaid in 40 states (the company has applied for Medicaid coverage in all 50 states). Insurance coverage of FAMILION testing increased dramatically in 2007–2008, with the number of covered lives growing from 7–155 million lives. By the end of 2009, this number had reached 280 million.

- It's not entirely clear what effect multiple test providers would have had on payer reimbursement in the early years. Multiple providers may have hastened favorable coverage decisions, although all of the genetic testing providers we spoke with readily admitted that obtaining third-party payer coverage is a lengthy and difficult process. PGxHealth's would-be competitor BRLI believes that its own recent aggregation of LQTS gene IP has prompted PGxHealth to more aggressively pursue insurance coverage.
- Having competitors may or may not have led to substantial improvements in quality and coverage, but we believe that a competitive presence could have accelerated the test to market and lowered the cost from $5400. BRLI, an admittedly biased party, asserts that earlier competition would have forced providers to differentiate the test to survive by developing newer platforms along with more patient and clinical support and education.
- Our understanding of LQTS genetics remains woefully incomplete. The same mutation in different members of the same family may lead to radically different phenotypes (or to no detectable signs or symptoms). This suggests the existence of yet-to-be discovered modifier genes and environmental factors. Meanwhile, some 10% of familial LQTS patients are presumptive compound heterozygotes, that is, they carry two distinct variations in LQTS susceptibility genes. This raises difficult clinical questions about which of these variants are pathogenic and which are benign. We believe it is legitimate to ask if the field as a whole might not have made deeper inroads into understanding the clinical significance of those uncertain variants if there were one or more additional commercial entities focused on the same sorts of interpretive questions.
- The results of genetic testing may have profound downstream financial implications. Both cardiologists and manufacturers of implantable cardioverter defibrillators stand to benefit from the implantation of such devices in actual or suspected LQTS patients.
- Conflicts of interest abound in this case study. These conflicts affect not only officers of PGxHealth and its primary consultant physician–scientist but also former, present and would-be providers of LQTS genetic testing.

WHAT IS LONG QT SYNDROME?

Congenital long QT syndrome (LQTS) is an inherited cardiac disorder affecting about 1 in 3000 to 1 in 5000 people. LQTS patients may experience fainting (syncope), seizures, or sudden death, although the phenotype can vary widely.[1] Most of the 1 in 2000 people harboring mutations in LQTS susceptibility genes will remain silent carriers throughout their lives.[2] That is, there are more people who have mutations in relevant genes than people who actually have a clinical syndrome. Nevertheless, the disease appears to explain a small but significant fraction of sudden cardiac deaths in young people.[2–4] Moreover, some 5% of cases of sudden infant death syndrome (SIDS) are thought to be attributable to familial or sporadic LQTS.[5]

The "QT" in long QT refers to a telltale measurement seen on an electrocardiogram (ECG). The QT interval is the time it takes for the heart to recharge (repolarize) after each beat. Depending on age and gender, when the corrected QT interval (QTc) exceeds ~440–470 milliseconds, it is considered to be prolonged. A prolonged QT interval coupled with a clinical history of fainting and a family history of LQTS or unexplained sudden cardiac death strongly suggest a diagnosis of LQTS.[1]

Clinical manifestations of LQTS are the result of the heart "spinning out of control" into a characteristic tachycardia (speeding of the heart rate) called torsades de pointes. Torsades de pointes cause an individual to faint; he or she may then wake up, experience seizures, or die. Survival then depends on whether the heart spontaneously assumes its normal rhythm or an internal or external defibrillator stops the arrhythmia.[6]

High-risk patients are typically treated with beta-blocker drugs, which can reduce the risk of life-threatening cardiac events.[1,2,7] Implantable cardioverter defibrillators (ICDs) may be used as a primary therapy in patients refractory to beta-blocker therapy or as a secondary measure in addition to beta-blockers.[8–10] Surgical denervation and pacemakers have also been used with some success.[1,11]

Although LQTS with accompanying deafness (Jervell and Lange-Nielsen Syndrome [JLNS]) and the classical form of the disease (LQT1, Romano-Ward Syndrome) were described more than 40 years ago, the exact molecular basis of the disorder eluded investigators until 1995.[1,6,12–14] It was then that Mark Keating's NIH-funded group at the University of Utah isolated genes predisposing to LQT2 and LQT3. With the cloning of these genes and the isolation of the *LQT1* gene the next year,[15] it became clear that defects in cellular sodium and potassium ion channels (or related proteins) caused LQTS: the window into the "cardiac channelopathies" was now open.[16] Currently, there are 12 known LQTS susceptibility genes,[17,18] although the QTc phenotype can vary and mutations in several genes have been observed in only a few families. Of the 12 genes, mutations in those predisposing to LQT1 (potassium channel gene, *KCNQ1*), LQT2 (potassium channel gene, *KCNH2*), and LQT3 (sodium channel gene, *SCN5A*) account for some 70% of congenital LQTS.[17]

Intellectual property and LQTS testing: *dramatis personae*

The following list (presented alphabetically) is intended to provide capsule descriptions of many of the important stake-

holders in and narrators of the LQTS genetic intellectual property (IP) story through early 2009. Some may have a conflict of interest by virtue of past and/or present consultation with genetic diagnostic test providers and/or past, present, or future provision of such testing themselves.

Dr. Michael J. Ackerman is Professor of Medicine, Pediatrics and Pharmacology at the Mayo Clinic. He directs the Mayo Clinic Windland Smith Rice Sudden Death Genomics Laboratory. He is Director of the Mayo Clinic's LQTS Clinic and is active in clinical translational research efforts devoted to identifying individuals at greatest risk for sudden death. He served on the Genaissance Pharmaceuticals Advisory Board in 2004[19] and is a paid consultant to FAMILION® test provider PGxHealth (M. Ackerman, Mayo Clinic, personal communication, 2008). He is a strong advocate of exclusive patent licenses for genetic diagnostics. Dr. Ackerman offers a charity waiver and conducts research-based genetic testing for patients unable to pay for FAMILION testing (M. Ackerman, personal communication, 2008).

Dr. Charles Antzelevitch is the Executive Director and Director of Research at the Masonic Medical Research Laboratory (MMRL). He also holds an academic appointment as Professor of Pharmacology at the SUNY Health Science Center at Syracuse and an endowed chair in Experimental Cardiology (Gordon K. Moe Scholar) at the MMRL. Dr. Antzelevitch provides free testing for hardship cases and enrolls patients in genetic research studies at the MMRL (C. Antzelevitch, MMRL, personal communication, 2008). He opposes exclusive patent licenses in the realm of genetic diagnostics (C. Antzelevitch, personal communication, 2008).

Dr. Sherri J. Bale is cofounder, President, and Clinical Director of GeneDx, a firm that specializes in genetic testing for rare hereditary disorders. Dr. Bale is a Board-certified PhD Medical Geneticist and a founding member of the American College of Medical Genetics. GeneDx offered partial genetic testing for LQTS until 2002, when it was sued by then-LQTS patent-licensee DNA Sciences. The two companies reached an agreement whereby GeneDx would refrain from offering LQTS testing (Appendix 7). In 2006, GeneDx was purchased by BRLI, which has since sought to offer genetic testing for LQTS (M. Grodman, BRLI, personal communication, 2008).[20] Dr. Bale is a strong opponent of exclusive licensing of gene patents for genetic diagnostic purposes, except as a tool to combat other exclusive licensing.

Congressman Howard L. Berman (D-CA) chaired the October 2007 Congressional hearing, "Stifling or Stimulating—The Role of Gene Patents in Research and Genetic Testing," under the auspices of his chairmanship of the House Judiciary Subcommittee on Courts, the Internet, and Intellectual Property.[21]

The Cardiac Arrhythmias Research and Education Foundation, Inc. (C.A.R.E.) is a 501(c)(3) nonprofit corporation based in Washington State. It advocates increased support for comprehensive scientific research and clinical trials; educates patients, public, and health professionals to increase awareness; and advances strategies to identify, protect, and support at-risk individuals and their families. Its Board of Directors includes Dr. Arthur J. Moss. Its Scientific Advisory Board includes LQTS experts Dr. Michael J. Ackerman, Dr. Charles Antzelevitch, Dr. Mark T. Keating, Dr. Dan M. Roden, and Dr. Jeffrey A. Towbin, among others.

Dr. Wendy K. Chung is a clinical and molecular geneticist who directs the clinical genetics program at Columbia University and performs human genetic research. She directs research programs in human genetics of complex traits. Clinically, she directs programs in risk assessment for oncogenetics, cardiomyopathy, arrhythmias, and diabetes and develops novel molecular diagnostic methods to improve genetic testing. She was formerly a member of the PGxHealth FAMILION Advisory Board (C. Reed and B. Salisbury, Clinical Data, personal communication, 2008). She is now a paid consultant to BRLI (W. Chung, Columbia University, personal communication, 2008). She submitted written testimony to the October 2007 Congressional hearing, "Stifling or Stimulating—The Role of Gene Patents in Research and Genetic Testing." Dr. Chung is a strong critic of exclusive patent licenses in genetic diagnostics.[22]

Mr. Drew Fromkin has served as President and Chief Executive Officer of Clinical Data since 2006. Clinical Data is the parent company of PGxHealth, which, from 2005 to 2009 was the exclusive provider of commercial genetic testing for LQTS. In April 2008, Mr. Fromkin submitted a letter to Congressman Berman responding to the 2007 Congressional testimony presented by Clinical Data's competitor BRLI.[20,23] Mr. Fromkin is a strong advocate of exclusive patent licenses for genetic diagnostics.[23]

Dr. Jorge Goldstein is an attorney at Sterne Kessler Goldstein and Fox. He has prepared and prosecuted patent applications before the United States and foreign patent offices in genomics, molecular and cell biology, recombinant DNA technology, immunology, transgenics, and therapeutic methods and in organic synthesis, pharmaceuticals, and polymers. He has written about patents and genetic diagnostics.[24–26] He serves as outside counsel to BRLI.

Dr. Marc Grodman founded BRLI in 1981 and has remained its Chairman of the Board, President, Chief Executive Officer, and a Director. Dr. Grodman is an Assistant Professor of Clinical Medicine at Columbia University's College of Physicians and Surgeons and Assistant Attending Physician at New York Presbyterian Hospital. He gave testimony at the October 2007 Congressional hearing, "Stifling or Stimulating—The Role of Gene Patents in Research and Genetic Testing."[20] BRLI has made inquiries about purchasing Clinical Data's laboratory operations and begun to aggregate LQTS gene IP (J. Goldstein, Sterne, Kessler, Goldstein & Fox, personal communication, 2008).[23] Dr. Grodman is a strong critic of exclusive patent licenses in genetic diagnostics, except as a tool to combat other exclusive licensing (M. Grodman, personal communication, 2008).[20]

Dr. Richard Judson was Chief Science Officer at Genaissance Pharmaceuticals from 1999–2005 and oversaw the commercial launch of FAMILION testing in 2004.

Dr. Mark T. Keating elucidated the genetic basis of LQTS in the mid-1990s at the University of Utah and is the principal inventor on several LQTS gene patents, including those covering the most common variants.

Mr. Steven Lehrer was CEO of DNA Sciences, the original licensee of the relevant LQTS gene IP, from 2001–2003. During his tenure as CEO, DNA Sciences filed suit against GeneDx for infringement of LQTS patents. Mr. Lehrer supports exclusive patent rights for genetic diagnostic tests.

Dr. Aubrey Milunsky is Professor of Human Genetics, Pediatrics, Obstetrics and Gynecology, and Pathology, and Founding Director of the Center for Human Genetics at Boston University (BU) Medical Center. The Center for Human Genetics is an international referral center for commercial DNA diagnostics and prenatal genetic diagnosis. Dr. Milunsky is board-certified in Internal Medicine, Pediatrics, and Clinical Genetics. BU began offering LQTS genetic testing in 2002. Since then, Dr. Milunsky has sought to offer prenatal and other commercial genetic testing for LQTS. He is a strong critic of

exclusive patent licenses for genetic diagnostics (A. Milunsky, Boston University, personal communication, 2008).

Dr. Arthur J. Moss is Professor of Medicine and Professor of Community and Preventive Medicine at the University of Rochester Medical Center. He is Director of the Heart Research Follow-up Program. His clinical research relates to cardiac arrhythmias and heart failure complicating chronic ischemic heart disease caused by coronary atherosclerosis. With Dr. Peter Schwartz, he cofounded the International Long QT Registry in 1979.[27] He was a member of the Genaissance Advisory Board[19] and consulted for the company before its sale to Clinical Data (A. Moss, University of Rochester, personal communication, 2008). At one time, he contemplated setting up commercial testing for LQTS at Rochester. He was later asked to consult by BRLI but declined (A. Moss, personal communication, 2008). BRLI funds LQTS-related research at the University of Rochester. Dr. Moss believes that gene patent licensing exclusivity is not in the best interests of society (A. Moss, personal communication, 2008).

Dr. Silvia G. Priori is Director of Molecular Cardiology and Electrophysiology Laboratories, Istituto di Ricovero e Cura a Carattere Scientifico Fondazione Salvatore Maugeri, Pavia, Italy. She is a clinical cardiologist specializing in the field of inherited arrhythmia syndromes. Much of Dr. Priori's research has focused on the genetic component of cardiac defects. She maintains a public database of LQTS mutations. In 2008, she began working part-time at New York University Medical Center. She has met with PGxHealth representatives and encouraged them to solicit input from additional physicians and scientists working in LQTS (S. Priori, Istituto di Ricovero e Cura a Carattere Scientifico Fondazione Salvatore Maugeri, personal communication, 2008).

Dr. Carol Reed is Executive Vice President and Chief Medical Officer for Clinical Data, Inc. From 2003–2005, she served as Vice President of Medical Affairs for Genaissance Pharmaceuticals. Dr. Reed is a strong advocate for exclusive patent licenses in genetic diagnostics.

Dr. Heidi Rehm is Associate Molecular Geneticist at the Harvard Medical School-Partners HealthCare Center for Genetics and Genomics. She is also Instructor in Pathology (Brigham and Women's Hospital), Director of the Clinical Molecular Genetics Training Program (American Board of Medical Genetics/Harvard Medical School), and Associate Director of the Harvard Medical School Center for Hereditary Deafness. Her clinical role involves daily sign out of hearing loss and cardiovascular disease testing for the Laboratory for Molecular Medicine in addition to an administrative role in overseeing the laboratory. We consulted with her on the evolution of commercial genetic testing for hypertrophic cardiomyopathy (HCM).

Dr. Hugh Y. Rienhoff founded DNA Sciences (originally Kiva Genetics) in 1998, serving as its Chairman and CEO until late 2001. He helped to negotiate the original LQTS gene patent licenses from the University of Utah. He is a clinical geneticist and holds an appointment in the Department of Molecular Biology and Genetics at The Johns Hopkins University School of Medicine. He is also the founder of MyDaughtersDNA.org, an organization dedicated to rare genetic conditions.

Dr. Dan M. Roden is Director of the Institute of Experimental Therapeutics, William Stokes Professor of Experimental Therapeutics, Professor of Medicine, and Professor of Pharmacology at Vanderbilt University. He has treated LQTS patients and performed research on the disease for many years. He holds a patent on a variant associated with drug-induced LQTS that he and his coinventor have licensed to Clinical Data, Inc. He told us he would be "happy" to give up his royalties if it meant improved patient care (D. Roden, Vanderbilt University, personal communication, 2009).

Dr. Benjamin A. Salisbury is Senior Director of Clinical Genetics for Clinical Data, Inc. He previously served as Group Leader for Computational Genomics at Genaissance Pharmaceuticals.

The Sudden Arrhythmia Death Syndromes Foundation (SADS) is a 501(c)(3) nonprofit corporation dedicated to informing the general public (as well as families and medical professionals) about the effects of untreated/undiagnosed cardiac arrhythmias and the methods by which sudden death can be prevented. Initiatives include sponsoring public awareness meetings in local communities, providing educational videos on LQTS, and establishing media relationships to publicize information about arrhythmias. SADS receives financial support from Clinical Data, Inc. Its Board of Trustees includes Drs. Michael J. Ackerman and Silvia G. Priori. Its Scientific Advisory Board includes Drs. Charles Antzelevitch, Dan M. Roden, Peter Schwartz, Jeffrey A. Towbin, Arthur Wilde, and Raymond Woosley.

Dr. Jeffrey A. Towbin is Professor in the Departments of Pediatrics (Cardiology), Cardiovascular Sciences, and Molecular and Human Genetics at Baylor College of Medicine (BCM). He is Chief of Pediatric Cardiology at Texas Children's Hospital, holds the Texas Children's Hospital Foundation Chair in Pediatric Cardiac Research, and is Director of the Phoebe Willingham Muzzy Pediatric Molecular Cardiology Laboratory. He is Medical Director of the John Welsh Cardiovascular Diagnostic Laboratory and of the Pediatric Heart Failure and Transplantation Service. He is Co-Director of the Cardiovascular Genetics Clinic at Texas Children's Hospital and Director of Research in the BCM Department of Pediatrics (Cardiology). For the last several years, Dr. Towbin's laboratory has offered fee-for-service cardiovascular genetic testing (J. Towbin, BCM, personal communication, 2008). These services include testing for mutations in *KCNJ2* (Andersen syndrome/LQT7 and short QT syndrome) and caveolin-3 (LQT9),[28] both of which are rare.[1,2] Dr. Towbin only offers testing for mutant genes that have been discovered by his laboratory; he has not patented any of these genes (J. Towbin, personal communication, 2008). The University of Utah Technology Commercialization Office owns the patent rights to the major LQTS susceptibility genes. Pursuant to the Bayh-Dole Act,[29,30] this office licensed rights to diagnostic testing of these genes to DNA Sciences in the late 1990s. Patent licenses were subsequently transferred to Genaissance Pharmaceuticals (circa 2003) and Clinical Data, Inc. (circa 2005).[31–35] During 2006–2008, Utah began licensing patent rights to certain LQTS susceptibility genes to Clinical Data competitor BRLI, thereby creating a potential mutual-blocking situation (J. Goldstein, personal communication, 2008).[24] Despite repeated requests, the University of Utah Technology Commercialization Office declined to speak with us while the case study was being prepared. It did consent to an interview in March 2009, but volunteered no materially relevant details about patents or licenses (for this study or for the BRCA case study, in which it is also involved).

Why is genetic testing for LQTS important?

Genetic testing for LQTS is clinically important for several reasons:

- For unequivocal diagnosis of LQTS, it remains the gold standard (W. Chung, personal communication, 2008),[36,37] although the resting ECG is critical and a negative genetic test cannot rule out the presence of the disease.[1,38]

- The consequences of relying solely on clinical history and sometimes imprecise and difficult-to-interpret ECG measurements for diagnosis can be grave. Twenty-five to 50% of genetically proven LQTS patients do not exhibit a pathologically prolonged QTc.[39] If not treated, LQTS-mutation carriers not identified by ECG/clinical evaluation have a 10% risk of a serious cardiac event by the age of 40 years.[40] Conversely, a recent study suggests that LQTS may be overdiagnosed; among a cohort of 176 patients referred to the Mayo Clinic for LQTS, 40% left the clinic without such a diagnosis.[41] Such patients who do not truly have LQTS may be given unnecessary beta-blockers or, worse, implanted with gratuitous ICDs.
- Management of LQTS can be genotype dependent.[1,42,43] LQT1 mutation carriers are more likely to experience syncope or sudden death in response to emotional or physical stress.[44] For LQT2 patients, cardiac events can be triggered by sudden loud noises.[45] Women with LQT2 mutations are at higher risk for cardiac events during the postpartum period.[46] Thus, genotype-specific management of the environment can be critical. Mutation location within a gene can be an important correlate of severity.[47] Moreover, beta-blocker therapy appears to be more effective in LQT1 patients[48] and may be counterproductive in LQT3, in which the lower heart rate is associated with an increased risk of arrhythmias (W. Chung, personal communication, 2008). In LQT3, the trigger often occurs during rest, whereas both LQT3 and JLNS are more often associated with fatal outcomes.[49]

Despite these arguments in favor of genetic testing, our understanding of LQTS remains incomplete. First, it must be emphasized again that a negative genetic test does not rule out a LQTS diagnosis. Second, because it is not always clear that a given variant in a LQTS gene causes disease, the potential for false positive diagnoses remains.[41] Finally, within a family, the same mutation may be associated with radically different severity and type of symptoms.[50] At the moment, genetic testing for LQTS appears to be most useful: (1) when a clinical diagnosis is fairly certain and treatment strategies may depend on the nature of the mutation or (2) to confirm or rule out the diagnosis in family members of an affected proband with a known mutation.[2] Clinical Data believes that testing may also clarify the clinical status of patients lacking a clear diagnosis (C. Reed and B. Salisbury, personal communication, 2008), although one clinician told us that the net effect of this approach can "open a can of worms" and leave patients without diagnoses and with variants of uncertain significance (D. Roden, personal communication, 2009).

The major European and American cardiology societies have issued joint guidelines for the care of patients at risk for sudden cardiac death, including those with LQTS.[51] Genetic testing is recommended for diagnosed LQTS patients. The Sudden Arrhythmia Death Syndromes Foundation (SADS) suggests genetic testing for:

- All patients with a diagnosis of LQTS who have not had a genetic test;
- Anyone tested in a research study with family members yet to be tested; or
- Family members of a LQTS patient known to carry a mutation.[52]

(Clinical Data has supported SADS financially since the company acquired rights to the major LQTS susceptibility genes in 2005. According to its annual reports available online, SADS received funding from Genaissance Pharmaceuticals, the previous exclusive licensee of the major LQTS gene patents, before 2005.[53])

Finally, we note additional incentives for genetic testing. Both cardiologists and makers of ICDs may financially benefit from the implantation of defibrillators in actual or suspected LQTS patients. Data indicate that ICDs are a cost-effective means of preventing sudden cardiac death when clinically indicated.[10] The dollars involved in ICD procedures dwarf those associated with genetic testing. Final ICD costs in 2007 sometimes approached $40,000.[54]

Genetic testing for LQTS: 1995–2004

After the identification of the first LQTS susceptibility genes, academic laboratories began offering genetic testing on a research basis. Clinicians whom we spoke to said that research subjects would often not receive their LQTS genotypes for a year or more (M. Ackerman and A. Moss, personal communication, 2008), if at all (J. Towbin, personal communication, 2008).

In 2001, GeneDx began offering commercial genetic testing for LQT1, LQT2, LQT3, LQT5, and LQT6. BU began testing the following year; both the laboratories also offered prenatal testing. As described in Appendix 8, the GeneDx LQTS testing regime was incomplete: it covered about one third of the combined coding regions of the five most important susceptibility genes (B. Salisbury, personal communication, 2008).[55–58] BU's assay was similar but not identical: it covered 26 of 63 exons in the five genes (A. Milunsky, personal communication, 2008).[58,59] At the time, there was a tacit assumption that LQTS would resemble cystic fibrosis with respect to mutation distribution, i.e., one or a few major mutations accounting for most of the disease burden plus a fair number of rarer mutations.[60] This turned out not to be the case; the overwhelming majority of LQTS mutations are "private" and not recurring (J. Towbin, personal communication, 2008).[2,47]

In an e-mail, the Mayo Clinic's Dr. Michael J. Ackerman, LQTS expert clinician, researcher, and consultant to PGxHealth, emphasized that during this period, there were a substantial number of misdetections and a high false negative rate (i.e., people with mutations causing LQTS but missed by genetic testing methods). He contends that BU, for example, marketed its test as equivalent to his own laboratory's research-based test, despite the former missing more than 30% of the mutations found by the latter. He believes that this confused doctors and patients because they thought the then-commercially available tests were equivalent to the Mayo test (M. Ackerman, personal communication, 2008). In his view, this period represented the "black hole" era in LQTS genetic diagnostics (M. Ackerman, personal communication, 2008).

Genetic testing for LQTS: 2004 to early 2009

Since its commercial launch by Genaissance Pharmaceuticals under the name FAMILION in 2004 and through early 2009, the genetic testing protocol for LQTS has remained relatively unchanged. (In this report we do not consider other cardiac-related FAMILION tests offered by Clinical Data subsidiary PGxHealth, including tests for arrhythmogenic right ventricular cardiomyopathy, Brugada syndrome, catecholaminergic polymorphic ventricular tachycardia [CPVT], and HCM.) Genaissance was purchased by Clinical Data, Inc., in 2005. As outlined in Appendix 1, a physician or laboratory collects a small blood sample (8 mL) from a LQTS or potential LQTS patient (the index case) and sends it to Clinical Data subsidiary PGxHealth

in New Haven, CT. On arrival, genomic DNA is extracted from blood, and the samples are barcoded for tracking.

Using primers specific for the tested genes, DNA samples are then amplified by polymerase chain reaction for direct sequence analysis of the susceptibility genes for LQT1 (the *KCNQ1* gene), LQT2 (*KCNH2*), LQT3 (*SCN5A*), LQT5 (*KCNE1*), and LQT6 (*KCNE2*) and as of 2009, several more genes. This analysis includes comprehensive sequence determination and variant detection in open reading frames and intronic sequences containing splice junction sites for the included exons. Through 2008, FAMILION testing for LQTS covered ~13.4 kb of DNA divided among 73 amplicons (B. Salisbury, personal communication, 2008). Directed sequencing is performed in both directions, except where the DNA sequence constraints preclude this approach (those regions are amplified and sequenced twice in a single direction). The DNA fragments resulting from polymerase chain reaction are electrophoretically separated and sequenced. Sequence traces are analyzed for heterozygous or homozygous variants by comparing with public reference sequences that have been confirmed by sequencing several hundred healthy individuals of diverse ancestry. Two technologists independently score all traces for variants, and a supervisor reconciles any discrepancies.

Mutations in five genes account for ~75% of clinically verified familial LQTS cases.[1,38] Actual yield from FAMILION testing has been substantially lower.[61] This lower yield is likely because of the inclusion of patients with a lower pretest probability of actually having LQTS (C. Reed and B. Salisbury, personal communication, 2008).[62,63] Surveillance of fewer genes by FAMILION testing versus research laboratories may have also played a role in determining yield.

As described in the FAMILION Technical Specifications Sheet (Appendix 1), reported variants are divided into Classes I, II, and III:

Class I: Deleterious and probable deleterious mutations
1. Evidence of deleteriousness
2. Nonsense variant
3. Missense single-nucleotide variant not seen in the reference panel in transmembrane-spanning domain or pore
4. Insertion or deletion
   a. Frameshift variant
   b. In-frame variant in transmembrane-spanning domain or pore

Class II: Possible deleterious mutations (variants of uncertain significance)
1. Missense single-nucleotide variant not seen in the reference panel and not in transmembrane-spanning domain or pore
2. Missense single-nucleotide variant seen in the reference panel with allelic frequency $<0.5\%$ but with published evidence of deleteriousness
3. In-frame insertion or deletion not in transmembrane-spanning domain or pore
4. Predicted splice-site variant

Class III: Polymorphisms (variants not generally expected to be deleterious)
1. Protein-altering variant seen in the reference panel with either
   a. Common frequency ($\geq 0.5\%$) or
   b. Rare frequency ($<0.5\%$) and without published evidence of deleteriousness

The final report is reviewed and signed by a CLIA-licensed (CLIA of 1988, which were designed to improve the quality and expand federal oversight of clinical laboratories in the United States[64]) Laboratory Director. Results are returned to the physician "usually within 6 weeks."[65] When a Class I or Class II mutation is found, a recommendation for clinical evaluation and genetic testing of first-degree blood relatives is included in the report (Appendices 2 and 3). Examples of a negative report and the accompanying letter sent to doctors are shown in Appendices 4 and 5, respectively. If the clinical interpretation of a reported variant changes, an amended test report is generated and provided to the referring physician when possible (Appendix 1).

The test costs $5400 for the index case and $900 to confirm/rule out a previously characterized mutation in each additional family member. PGxHealth maintains a customer service group that works with patients' insurance providers to preauthorize services. PGxHealth is quoted an estimate of coverage from the insurance carrier but does not guarantee reimbursement.[66]

LQTS genes: the IP chain of custody

Insofar as we can tell, until fairly recently, the IP attached to the major LQTS susceptibility genes was exclusively licensed by the University of Utah to a succession of corporate genetic testing firms, but at any given time, exclusive rights were held by a single firm. (The University of Utah Technology Commercialization Office declined to speak with the authors on the record, despite repeated requests until March 2009, when the case study was complete. Utah did not disclose relevant information about patents and licenses in that brief interview.) DNA Sciences, Inc., was the original sole licensee (1999–2003; H. Rienhoff, founder and former CEO of DNA Sciences, personal communication, 2008). In 2003, most of the assets of DNA Sciences, including patent licenses for the three major LQTS genes, were purchased out of bankruptcy by Genaissance Pharmaceuticals (R. Judson, former CSO of Genaissance Pharmaceuticals, personal communication, 2008), which, after renegotiation of the patent licenses, launched commercial LQTS testing in 2004 under the name FAMILION.[35] In 2005, Genaissance was acquired by Clinical Data, Inc.[31]

Since that time, Clinical Data subsidiary PGxHealth" has overseen rapid growth in commercial testing for LQTS and other channelopathies. In fiscal 2008, sales of PGxHealth tests grew 41% year-over-year to $4.6 million. Judging from a company presentation,[67] the overwhelming source of this growth was FAMILION testing (for LQTS, CPVT, and Brugada syndrome). LQTS notwithstanding, Clinical Data has licensed rights to these other cardiac disorders on a nonexclusive basis. In May 2008, the company launched a test for HCM. During the same year, the company launched a provider-focused sales force and customer-service staff to help drive FAMILION test adoption,[68] to which much of the sales growth can be attributed, along with an increased focus by PGxHealth in working with physicians to convince reluctant insurers to cover genetic testing for LQTS. PGxHealth reported that it has also invested in enhancements in its laboratory operations to handle the increased volume and to reduce turnaround times (C. Reed and B. Salisbury, personal communication, 2008). According to BRLI CEO Dr. Marc Grodman, the intention of his company to enter the cardiac genetics market became well known by early 2007. He believes this potential competition played an important role in Clinical Data's marketing strategy (M. Grodman, personal communication, 2008).

Genetic testing for LQTS: at issue

Questions about LQTS IP came to the fore and achieved policy significance through the 2007 Congressional testimony

of BRLI CEO Dr. Marc Grodman and Columbia University clinical geneticist Dr. Wendy Chung.[20,22] In their testimony they contended that:

- Competition in diagnostic testing is critical to the public health; because of exclusive licensing of the relevant gene patents in LQTS, there is effectively no competition, and there has not been since 2002.
- The discovery of the LQTS genes was partly funded by National Institutes of Health, yet, the University of Utah had originally, and at the time of Dr. Grodman's testimony, only seen fit to license the patents to a single private-sector provider.
- By sending cease-and-desist letters to and/or suing the laboratories who were offering LQTS genetic testing before commercialization and refusing to sublicense to any other genetic test provider, DNA Sciences, Inc. (the exclusive patent licensee at the time), created a nearly 2-year period during which only research laboratory-based testing was available to LQTS patients and family members. During that period, DNA Sciences "cleared the market" of potential competitors, including nonprofit testing services, although DNA Sciences did not yet offer a test itself.
- LQTS genetic research has been stifled by Clinical Data's monopoly.
- There have been problems with quality and interpretation of results in Clinical Data's LQTS testing.
- Clinical Data has not developed the ability to reliably perform genetic testing on paraffin-embedded samples from deceased persons.
- Clinical Data's testing regime is incomplete.
- Clinical Data's turnaround time can be as long as 6–8 weeks.
- Variants of unknown significance are disproportionately reported in minority populations.
- FAMILION testing is $5400; a competitive laboratory could offer the test for about "a quarter of the price." The cost of the test is "not routinely covered by most insurance companies without a lengthy preauthorization process that frequently takes 3–12 months to complete." The test would be accessible to many more patients if it were "correctly" priced in a competitive marketplace.

In an April-2008 letter to Howard L. Berman (D-CA), Chairman of the House Judiciary Subcommittee on Courts, the Internet, and Intellectual Property, Clinical Data CEO Drew Fromkin responded to the Grodman/Chung testimony.[23] In his letter, Fromkin argued:

- The patent system and the availability of exclusive licensing spurs innovation and provides incentives for product development that can save lives. LQTS is a great example.
- Clinical Data is highly motivated to continually improve FAMILION testing: the company has reduced turnaround time from 6 weeks to 4.5 weeks. With or without competition, poor products stop selling.
- Clinical Data periodically considers adding LQTS mutations to its testing regime. Recently, the susceptibility gene for CPVT was added to the FAMILION menu.
- In most cases so far, the inclusion of additional genes would add cost to the test with only minimal clinical benefit.
- Research has not been stifled: since the launch of FAMILION testing, four new LQTS genes have been identified. In the event of a FAMILION test comes back negative, the patient is referred to a research laboratory for further testing.
- Clinical Data are ready to accommodate any common specimen type, including paraffin-embedded tissues.
- Clinical Data holds itself to the highest federal and corporate standards for the quality of its laboratory work: two clear sequencing reads are required for every sample. All variants are reviewed by three people, including a board-certified medical geneticist.
- Clinical Data responds immediately to reports of inconsistent or erroneous reports.
- Clinical Data regularly presents its LQTS data at national meetings. Additional publications are in preparation.
- Without exclusive patent rights in this and most other fields, competitive pressures would severely limit the disclosure of scientific discovery and harm the public interest.
- Of >1300 non-LQTS individuals tested, mutation information has been published on >700 with more to come. This testing is done to quantify and specify background variation, so that the test specificity is understood and so that fewer rare, benign variants are mistaken for pathogenic mutations (C. Reed and B. Salisbury, personal communication, 2008).
- Half of the healthy subjects who have been tested have come from non-Caucasian populations.
- Health plan coverage of FAMILION LQTS testing has grown rapidly despite the fact that gaining insurance coverage is "a long and difficult road" that takes years.
- Exclusive licenses lead to higher quality genetic tests that in turn lead to better patient outcomes and a more cost-effective health care system. Nonexclusive rights lead to "commodity" and "me-too" tests that place pressures on profit margins, which result in mediocrity and can ultimately harm patients and society.
- Dr. Grodman has a financial interest in the nonexclusive licensing of LQTS gene patents. Moreover, he has approached Clinical Data in the past seeking: (1) a license to FAMILION tests and (2) to acquire Clinical Data's laboratory operations as a whole. Clinical Data are surprised he "would so quickly be transformed from a suitor to a harsh critic."
- Dr. Grodman's words do not match his actions. In early 2008, Dr. Grodman's company acquired an exclusive license to the patent surrounding the LQT7 gene (*KCNJ2*).

In October 2008, attorney Jorge Goldstein, counsel to BRLI, informed us that, since the time of the testimony of Dr Grodman (October 2007), his client had obtained licenses to several LQTS gene patents relating to LQT1, 2, 3, 5, 6, and 7. The patent landscape had, therefore, become divided between the licenses held by PGxHealth and those held by BRLI (see update in text box).

Given such highly polarized and seemingly contradictory assertions, LQTS is a natural case study for the effects of IP on access to genetic testing. Beyond the Grodman/Chung testimony and the Fromkin response, there are other reasons to undertake an examination of patenting in LQTS. First, with an incidence of 1 in 3000 to 1 in 5000,[1,2,17] it is a relatively common Mendelian disorder. Second, as in hereditary breast cancer testing, from the outset, there has been a single exclusive licensee of the major LQTS genes (at least until recently). However, there was a period before 2003 when the LQTS gene patent rights were not enforced; thus, we are able to compare the pre- and postenforcement landscapes, albeit in a highly limited way and with some very serious caveats. (BRLI's Dr. Grodman

believes that because of advances in technology since the early 2000s, this "then-and-now" comparison unfairly favor current applications. For their part, Clinical Data's Drs. Reed and Salisbury believe that the recent advances in genetic diagnostic technology, the relative completeness of the current commercial test, and the greater awareness of clinicians and patients of genetic testing also cast serious doubt on the validity of this comparison.) Third, genetic testing in LQTS matters: undiagnosed cases may be at high risk for cardiac events,[37,40] which could potentially be avoided if these individuals were known to carry a mutation in one or more specific genes. Moreover, different mutations in different genes may suggest different therapeutic options.[42,69,70]

LQTS GENES AND IP

Research, databases, publications, and technical issues

The field of LQTS genetics is still young. As with hereditary breast cancer, the molecular basis of the major LQTS genes has only been known since the mid-1990s.[12–15,71] The prospect of a Bayh-Dole act inspired patent incentive,[29,30] however, did not appear to stimulate a LQTS gene race akin to the race for the hereditary breast cancer genes,[72] probably because of the relative rarity of LQTS and what was presumed to be a small market for LQTS testing. The principal inventor on the LQTS gene patents, Dr. Mark Keating, a cardiologist then at the University of Utah, was himself skeptical about the commercial value of testing, although his laboratory was inundated with requests from other physicians to perform genetic tests on their LQTS patients. Dr. Hugh Rienhoff, the founder of DNA Sciences and a friend of Dr. Keating's, thought there would be commercial value beyond diagnosing LQTS mutations, namely, that SIDS might also be a part of the spectrum of LQTS and that variants in certain genes combined with particular drugs might induce LQTS. Consequently, DNA Sciences licensed the patents on LQTS genes and mutations with a view toward extending the research to include these new patients: SIDS victims and their families and individuals on drug regimens vulnerable to drug-induced LQTS resulting from certain genetic variants. The research into LQTS, thus, stemmed from Dr. Keating's very successful genetics research. DNA Sciences extended the LQTS paradigm into areas that Dr. Keating thought were likely to be more complicated and scientifically less productive. According to Dr. Rienhoff, Keating was "more or less right about that" (H. Rienhoff, personal communication, 2008).[5] Dr. Rienhoff said there was also skepticism on the part of DNA Sciences investors as to whether genetic testing for "infrequent" (in commercial terms) congenital cardiac disorders would be a viable business (H. Rienhoff, personal communication, 2008).

Through 2008, there was no corporate equivalent in LQTS to the extensive Myriad Genetics contributions to the public BRCA mutation database.[73] Dr. Silvia Priori maintains a public, online database in Italy that includes "a couple thousand" LQTS patients; its mutation data are culled mainly from the published literature (S. Priori, personal communication, 2008). Drs. Arthur Moss and Peter Schwartz founded the International Long-QT Syndrome Registry in 1979; today it includes 1276 families and ~3600 affected or borderline-affected patients, with genetically confirmed diagnoses in ~2000 of those cases (A. Moss, personal communication, 2008).[1,27] Most of the Registry's genotype information, however, was obtained from research laboratories and not from FAMILION testing (A. Moss, personal communication, 2008); Drs. Reed and Salisbury suggested to us that this is because the Registry was closing around the time of the FAMILION launch in 2004. According to Baylor's Dr. Towbin, access to the Registry is by application (J. Towbin, personal communication, 2008). Before the FAMILION launch, Genaissance and Dr. Michael Ackerman from the Mayo Clinic collaborated to establish an internal database of normal controls and LQTS mutations (R. Judson, personal communication, 2008). Without associated clinical data, it is not clear to us how helpful access to the FAMILION mutation data would be. Dr. Towbin suggests that it is unreasonable to expect a nonresearch laboratory to acquire the necessary clinical data (J. Towbin, personal communication, 2008). However, BU's Dr. Aubrey Milunsky, director of BU's clinical genetics diagnostic service and a former and would-be LQTS testing provider, believes that a knowledge base of certain clinically useful and detailed phenotypic information can come only from a commercial diagnostic laboratory and not from research laboratories. Drs. Reed and Salisbury believe such registries should be set up under the auspices of an independent institution with Institutional Review Board approval, as Dr. Moss and Dr. Priori have done. PGxHealth, they say, would support such an initiative (C. Reed and B. Salisbury, personal communication, 2008). In November 2008, Clinical Data announced that its LQTS mutation data would be made public in spring 2009.[74]

To the best of our knowledge, during the FAMILION (Genaissance/Clinical Data) testing period from 2004–2008, there were three full-length LQTS articles published in which scientists employed by the corporate patent licensees shared authorship.[75–77] The companies also presented data at national meetings and published their findings in abstract form.[61,62,78–89] PGxHealth representatives informed us in June 2008 that the company had multiple manuscripts in progress (C. Reed, B. Salisbury, and M. Ackerman, personal communication, 2008). As noted in the update at the end of this report, those were published in 2009.

As noted in the Dramatis Personae section, Dr. Ackerman's group performs LQTS genetic research at the Mayo Clinic, as does Dr. Priori's in Pavia, Dr. Moss's in Rochester, Dr. Towbin's at Baylor, Dr. Roden's at Vanderbilt, and Dr. Chung's at Columbia University, among several others. It is clearly not in PGxHealth's interest to discourage or antagonize these investigators—the LQTS research community is fairly small, and these physicians are invaluable liaisons to patients. There has been productive collaboration between PGxHealth and these investigators, including in the interpretation of variants of unknown significance that may or may not cause disease. Dr. Ackerman is a paid consultant to Clinical Data, Dr. Chung is a paid consultant to diagnostic firms BRLI, and Dr. Moss has consulted for Genaissance in the past. In a few cases, however, test results and/or their interpretation appear to have differed (W. Chung and A. Moss, personal communication, 2008).[22] This is not surprising: virtually all laboratories make occasional errors,[90] even in cases where they are screening for the same few mutations over and over again.[91] However, in instances where discrepancies occur, it is conceivable, especially in a disease as challenging to understand as LQTS that the availability of a second commercial provider held to the same CLIA standards, motivated by the same incentives, and subjected to the same competitive pressures could offer a second source of variant confirmation (and perhaps alternative interpretation).

Clinical Data's Dr. Reed: "We encourage our customers to inform us if there is any question or concern regarding a result or an interpretation. We fully annotate our reports and will work to resolve any concerns. If a mistake on our part is found, we will rectify it and improve any process that might have been

faulty. In fact, if we are notified of a discrepancy we are obligated to resolve it" (C. Reed and B. Salisbury, personal communication, 2008).

"Reinterpreting a result would not require a second laboratory, just an expert, and/or new information. Research laboratories are generally headed by exactly the expert individual capable of sorting out discrepancies and/or differences in interpretation" (C. Reed and B. Salisbury, personal communication, 2008).

It is important to note again the existence of conflicts of interest on all sides. Those providing commercial testing (PGxHealth and its consultants) had an interest in maintaining the status quo. Many of those who would like to see other commercial providers and stand to benefit from becoming one of them (former providers, BRLI and its consultants) had an obvious interest in altering the current system.

The most important LQTS patents licensed to PGxHealth begin to expire in March 2015.[92] Until then, PGxHealth and recent licensee BRLI may exercise significant influence over the course of LQTS genetic research in the United States.

Clinical Data suggested to us that FAMILION testing might actually be facilitating research by identifying patients with known mutations, allowing research laboratories to focus their resources on those without known mutations. The company also emphasized that it does not prevent research laboratories from conducting research (C. Reed and B. Salisbury, personal communication, 2008).

To date, although we cannot know with certainty what might have been had there been multiple providers, we have no evidence that the virtual LQTS monopoly from 2003–2008 had a stifling effect on research, with the possible exception of interpretation of variants of unknown significance, which is discussed in subsequent sections.

Development and commercialization

The University of Utah Research Foundation was granted three patents covering the major genes predisposing to LQT1, LQT2, LQT3, and LQT5 in 1997, 2001, and 2002.[92–94] DNA Sciences received exclusive licenses to these patents beginning in 1999, under a "fairly standard" royalty agreement with the University of Utah Research Foundation (H. Rienhoff, personal communication, 2008). In 2003, Genaissance purchased most of the assets of DNA Sciences out of bankruptcy (R. Judson, personal communication, 2008).[95] In the first quarter of 2004, Genaissance concluded agreements with the University of Utah and Yale University covering an estate of more than 50 issued and pending patents relating to the five known mutant genes predisposing to cardiac channelopathies.[19] These agreements included an exclusive license to patents pertaining to the three major LQTS susceptibility genes that had been licensed to DNA Sciences (R. Judson, personal communication, 2008). The LQTS patent landscape as we understand it is presented in Appendix 6.

The LQTS gene patents were key assets of both DNA Sciences[32] (H. Rienhoff, personal communication, 2008) and then Genaissance (R. Judson, personal communication, 2008).[96] Clearly, there was perceived value in LQTS IP. Both Genaissance and Clinical Data appear to have made testing for LQTS a substantive part of their genetic testing business plans.[34,97] (Nota bene: Clinical Data has declined to share its current or past LQTS-related IP rights with us. We have partially deduced these holdings from interviews with former executives at DNA Sciences and Genaissance, from Securities and Exchange Commission filings, from litigation-related documents and cease-and-desist letters, and from an interview with BRLI's outside legal counsel.)

A patent infringement suit was brought by DNA Sciences against GeneDx in 2002 (Appendix 7). Patent enforcement letters were sent to one or more additional laboratories at around the same time (S. Lehrer and W. Chung, personal communication, 2008). This suggests an effort by DNA Sciences to "clear the market" in 2002. According to DNA Sciences founder Dr. Rienhoff (who left the company in 2001), one of the stipulations of the company's license agreement with the University of Utah was that the company vigorously defend its IP; not to do so would have been a violation of that agreement (H. Rienhoff, personal communication, 2008).

Because DNA Sciences had not yet developed the test when financial difficulties necessitated the sale of its assets to Genaissance in 2003, commercial testing was not offered until May 2004 with Genaissance's launch of FAMILION. Thus, it is likely that there was a period of 18 months or so during which genetic testing for LQTS testing was limited mostly to academic laboratories, whose turnaround time can be a year or more (A. Moss, personal communication, 2008).

Dr. Milunsky at BU reported Clinical Data's more recent efforts to prevent his laboratory from offering genetic testing for LQTS.[98] According to PGxHealth, this was because he had begun to offer the LQTS test more widely, versus only conducting LQTS research (C. Reed and B. Salisbury, personal communication, 2008).

Genaissance's launch of FAMILION testing for LQTS in May 2004[35] came 9 years after the first patent application was filed.[92] We speculate the delay was likely because of a combination of factors: the bursting of the biotech bubble in 2000 (H. Rienhoff, personal communication, 2008), the relative complexity and technical difficulty of the test,[77] and perhaps exclusive IP (which may have created less external competitive pressure on the licensee to launch, although it is possible that exclusivity increased investment up front, expediting product launch).

Genaissance (2004–2005) and Clinical Data subsidiary PGxHealth (2005–present) remained essentially the sole commercial providers from 2004–2008. (GeneDx was acquired by BRLI for $17 million in 2006.[99]) Dr. Milunsky's nonprofit, university-based laboratory offered testing until 2006. From 2006–2008, BRLI acquired exclusive licenses from the University of Utah for 13 patents related to composition of matter and/or mutation detection in LQT1, LQT2, LQT3, LQT5, LQT6, and LQT7 (Appendix 6). Thus, the LQTS IP began to fragment, with two licensees of different patents covering different genes and mutations.

The price for complete sequence-based FAMILION testing of five LQTS genes has remained $5400 since the 2004 Genaissance launch (C. Reed and B. Salisbury, personal communication, 2008). Payer coverage has increased significantly during these 5 years.[74] Clinical Data's Dr. Reed says that it is important to note that ". . . retail price does not directly correlate with revenue generated and cash received by a laboratory provider, including PGxHealth. Discounting to payers and inability to collect copayments/deductibles from patients leads to a notably lower value to the laboratory" (C. Reed and B. Salisbury, personal communication, 2008).

In 2002, GeneDx offered partial testing for $2200. GeneDx claimed that it could detect 87% of the mutations present in the genes for LQT1, LQT2, LQT3, LQT5, and LQT6 and that the overall sensitivity of its test was 59% (see Appendix 8). Given what has been learned about LQTS mutations since—namely that most mutations are "private" and not recurring[2,47]—GeneDx's sensitivity was probably significantly lower than that estimate. By our calculations, GeneDx was screening about 33% of the five genes' ~13.4 kb of combined coding sequence

(B. Salisbury, personal communication, 2008).[55–58,101] PGxHealth charges—and has always charged—$900 to confirm a mutation in additional family members; the same service was reportedly $350 from GeneDx and $250 from BU in 2002 (A. Milunsky and S. Bale, personal communication, 2008). The fact that GeneDx and BU both provided fee-for-service testing from ~2001–2002 before the patents were enforced suggests that a patent incentive was not required to develop a test (S. Bale and A. Milunsky, personal communication, 2008). Clinical Data's Dr. Reed argues that during this period, there is no evidence that GeneDx or BU invested in physician education or expanded insurance coverage for their "inferior" tests (C. Reed and B. Salisbury, personal communication, 2008).

LQTS testing uptake has grown steadily since 2004. Genaissance reported FAMILION revenues of $841,000 from the launch during May 2004 through June 30, 2005.[102,103] Subsequently, the test has been a consistent source of growth for Clinical Data. FAMILION sales grew from ~$2.7 million in fiscal 2007 to ~$4.5 million in fiscal 2008. In the first two quarters of fiscal 2009, FAMILION generated an estimated $4.1 million.[104] Dr. Reed notes her company's ". . . significant investment in Clinical Data's sales and marketing efforts, infrastructure and payer contracting. Furthermore, this increase could not have happened without the intensive investment by PGxHealth and collaborations with academia and advocacy groups . . ." (C. Reed and B. Salisbury, personal communication, 2008).

The fairness of the price of five-gene testing ($5400 or ~$74 per amplicon) is difficult to judge definitively given the exclusive license (and, therefore, no direct competitive comparison). It is worth noting that in 2002, if we assume one amplicon per exon, GeneDx charged ~$129 per amplicon ($2200) for its partial primary screen of 17 exons selected from the five genes. (In patients and families known to have JLNS, a rare autosomal recessive variant of LQTS that features profound congenital deafness, GeneDx screened for mutations in all exons of *KCNQ1* and *KCNE1*, the two susceptibility genes known to cause JLNS [see Appendix 8]). On the other hand, Myriad Genetics charges $38 per amplicon for its sequence-based testing of the *BRCA1* and *BRCA2* genes, for which it has exclusive rights (see BRCA case study in this volume) and a significantly higher test volume. In the course of preparing this case study, some patients, patient advocates, and physicians complained to us about the high cost of the FAMILION test and less than complete payer coverage, although incomplete coverage is not in Clinical Data's interest, either. Dr. Rienhoff and Mr. Lehrer, both formerly of DNA Sciences, emphasized the complexity of the test that eventually became FAMILION and said the price should be judged accordingly (S. Lehrer and H. Rienhoff, personal communication, 2008).

In his rebuttal to the Grodman/Chung testimony, Clinical Data CEO Drew Fromkin pointed out that Grodman's firm had recently secured an exclusive license on *KCNJ2*, the susceptibility gene for hereditary LQTS7, a rare form of the disease,[23] thereby suggesting that Grodman was being hypocritical. Grodman told us that his licensing of the gene was strategic. "We have exclusive licensing [on *KCNJ2* and some others], but we have not exercised it. We were approached by [Clinical Data] to do the [LQT7] test with them and we said we'd be happy to share IP. Part of that is strategic, it's not a belief in the process. It's not what you have, it's what you do with it" (M. Grodman, personal communication, 2008). Indeed, in the face of a preexisting exclusive license to a competitor, absence of a patent or a nonexclusive license would not solve the problem, and an exclusive license may be the only legal tool to compel cross-licensing or other negotiated agreement. Securing an exclusive license is, therefore, not necessarily hypocritical if it is a strategy to induce negotiation in the face of existing exclusive rights.

Dr. Reed regards this as ". . . an incomplete statement and somewhat self-serving. In fact, we approached Dr. Grodman to in-license his 'strategic' IP to run the test for this single gene ourselves, not with [BRLI]. Dr. Grodman would agree only if we cross-licensed the whole of our LQTS IP so [BRLI] could commercialize a directly competitive LQTS test. This was not an appealing proposition to us . . .. [This is] a business dispute where one party simply wants rights to a market the other company has built diligently through entrepreneurial investment of time and resources" (C. Reed and B. Salisbury, personal communication, 2008).

This case is, thus, a stark illustration of two features of how exclusive licensing of patent rights can influence diagnostic testing—the potential for mutual blocking situations—and the "penumbra effect" (discussed in the hearing loss case study also) in which exclusive rights to one or a few common genetic variants can in effect drive business for all genetic testing—even for variations that have been discovered but not patented or that have never been discovered before—to the rights holder. That is, rights on one set of mutations can be leveraged to drive business for other mutations not covered by patent claims. This has been the practice until very recently for LQTS testing.

In at least one instance, Clinical Data has sublicensed its LQTS IP. In October 2007, the company announced that its PGxHealth subsidiary had entered into a nonexclusive sublicense agreement with the Victorian Clinical Genetics Services, a not-for-profit subsidiary of the Murdoch Children's Research Institute, for the provision of genetic testing for familial LQTS in Australia and New Zealand.[105] According to Dr. Reed, this shows Clinical Data's ". . . willingness to cede markets to others where we are not equipped to provide services" (C. Reed and B. Salisbury, personal communication, 2008). However, this has minimal relevance to the US market, because it affects testing in a foreign jurisdiction covered by patent law in that jurisdiction.

PGxHealth has also availed itself of others' nonexclusive licenses. In May 2008, the company launched genetic testing for HCM, which has been licensed by Harvard Medical School to multiple diagnostic providers.[106] Drs. Grodman and Chung contend that HCM is a better model for IP related to genetic testing because it fosters a system of competition and checks and balances (W. Chung and M. Grodman, personal communication, 2008). Dr. Ackerman, on the other hand, pointed out that the test continued to lack both Medicare and Medicaid coverage in 2008 in most jurisdictions (M. Ackerman, personal communication, 2008). Dr. Heidi Rehm, Associate Molecular Geneticist at the Harvard Medical School-Partners HealthCare Center for Genetics and Genomics, confirmed this assertion (as did another provider off the record). She said that although Harvard launched the commercial HCM test in 2004, Harvard is proscribed from offering direct third-party billing (H. Rehm, personal communication, 2008). The second provider, Correlagen Diagnostics, did not launch until July 2007.[107] Dr. Reed says that by offering HCM testing, Clinical Data are ". . . [building] on the investment justified by our LQTS test" (C. Reed and B. Salisbury, personal communication, 2008).

Communication and marketing

In 2004–2005, Dr. Ackerman wrote at least four articles in professional journals that noted the availability of commercial

genetic testing for LQTS; his financial interest was disclosed in each case.[6,38,43,108] A 2005 article partially funded by Genaissance concluded that genetic testing for familial LQTS was cost-effective.[109]

Clinical Data has undertaken efforts to market its services to physicians. In 2007, the company established a sales force to promote FAMILION testing. This sales force makes calls on pediatric electrophysiologists and cardiologists and, increasingly, their adult equivalents. Based on the initial positive results of this effort, the company expanded the size of the sales force in 2008. Clinical Data has also added resources to focus on the provider and payer markets and has a dedicated customer service group (C. Reed and B. Salisbury, personal communication, 2008).[68]

PGxHealth also markets FAMILION testing via patient advocacy groups and professional organizations that offer patient support and promote research and education. These include the SADS, and "The National Society of Clinical Geneticists."[68] (The authors found no group named the "National Society of Clinical Geneticists." It's possible that this could be referring to the National Society of Genetic Counselors or the American College of Medical Genetics.)

Examining test quality

In five cases, Dr. Chung, a paid consultant to BRLI and former consultant to PGxHealth, said she split samples and tried to confirm PGxHealth's results in her own laboratory. In two cases, she said there were discrepancies. In one case, there was a sequencing problem; in the other, there was an informatics issue (W. Chung, personal communication, 2008).

In her 2007 statement to Congress and in interviews with us and the Secretary's Advisory Committee on Genetics, Health, and Society (SACGHS) Task Force on Gene Patents and Licensing Practices, Dr. Chung called PGxHealth's protocol for dealing with variants of unknown significance and other ambiguous results inadequate, especially given that 5–10% of all results will be difficult to interpret.[22] ". . . it puts clinicians in a very awkward position [if] the patient has spent $5400 on this test . . . and [the test providers] don't know how to interpret it . . ." (W. Chung, personal communication, 2008). Dr. Chung has expressed particular concern about the interpretation of so-called "Class II variants," which PGxHealth calls "variants of uncertain significance" and "possible deleterious mutations." These include some missense variants, in-frame deletions/insertions, and predicted splice-site variants (see Appendix 1). Dr. Chung expressed fear that many cardiologists will interpret these as definitive disease-causing variants (W. Chung, personal communication, 2008). Dr. Chung also contended that there has not been robust vetting of these variants because the scientific community did not have access to PGxHealth's database (W. Chung, personal communication, 2008).

Dr. Chung believes that having only a single commercial provider denies clinicians the opportunity to solicit a second opinion. ". . . when you don't have the ability to get a second opinion, you have no idea where your errors or pitfalls are and [there is] no independent way for clinicians to be able to validate whatever they're seeing or, on the other hand, to be able to come up with [what] at the end is a correct diagnosis" (W. Chung, personal communication, 2008). Dr. Milunsky, who is a past and would-be a provider of commercial testing, shares this view (A. Milunsky, personal communication, 2008). Their assumption is that multiple providers would reach consensus interpretations, and alternative providers would be accompanied by more public availability of data and more open to discussion of its interpretation.

Dr. Chung also criticizes PGxHealth for the incompleteness of FAMILION LQTS testing prior to 2009. She takes issue with Clinical Data's earlier contention that the addition of more genes to the FAMILION panel would not add much value. She says that this cannot be known with certainty (W. Chung, personal communication, 2008). Given that there are now two providers, which together now test for all 12 genes (see update), Dr. Chung's objections appears to have been borne out.

In her 2007 testimony, Dr. Chung stated that PGxHealth is not able to reliably offer genetic testing on paraffin-embedded tissue samples, which is often the only tissue sample available from deceased persons.[22] She told us about a case in which a patient was receiving a heart transplant in which the donor heart had LQTS; she described an "ordeal" to get PGxHealth to extract DNA from frozen tissue.[22]

By its own admission, PGxHealth's results have not been perfect. In biannual proficiency testing, "there has been an occasional conflict," although Dr. Reed emphasizes that in every such case, "we have been right" (C. Reed and B. Salisbury, personal communication, 2008).

Responses to quality concerns

Dr. Reed takes strong exception to Dr. Chung's claims: ". . . Dr. Chung [is] a paid consultant to a competitor company that desires access to the patents under discussion."

"These variants are inherently ambiguous and 'problematic.' This has nothing to do with 'protocols,' rather it is a matter of biomedical science where even experts may disagree. Just because we don't interpret every mutation the way Dr. Chung might, does not make it wrong. We acknowledge that this is a difficult area. Thus, Dr. Chung's concerns are no surprise and are indicative of the state of the art." Dr. Reed also notes that as a former member of a FAMILION Advisory Board, Dr. Chung has engaged herself in discussions with the company as to the difficulty in interpreting these variants. Dr. Reed also points out PGxHealth uses a reference population of >1300 controls to evaluate all variants (Appendix 1). This reference population, says Dr. Reed, plays a critical role in ensuring that variants are appropriately classified. Finally, with respect to including additional genes, Dr. Reed suggests that the lack of knowledge about these loci makes it ". . . premature to include these genes in a clinical test . . . [A]dding them could create more confusion for cardiologists and may decrease the clinical specificity of testing." Furthermore, she notes that Dr. Moss, as quoted in this report (see below), does not think it worthwhile to add genes with noncardiac syndromic manifestations that can be fairly easily diagnosed by physical examination (C. Reed and B. Salisbury, personal communication, 2008). Again, we note that PGxHealth has since added six genes to its test panel.

For proficiency testing of the FAMILION assay, Dr. Ackerman sends blinded, de-identified samples to PGxHealth every 6 months. According to him, since 2004, there has been only a single discordant result, which was attributable to his laboratory missing a nonsynonymous variant that PGxHealth detected (M. Ackerman, personal communication, 2008). Dr. Reed notes that these results are available via Clinical Data's periodically audited proficiency testing records (C. Reed and B. Salisbury, personal communication, 2008).

Again, one difficulty in evaluating the quality and proficiency FAMILION testing is the inherent conflict of interest of a number of the critical stakeholders. Dr. Ackerman, for example, is a paid consultant to Clinical Data. Dr. Chung is a paid consultant to Clinical Data competitor BRLI and former consultant to PGxHealth. Mr. Fromkin and Dr. Grodman are at the helms of the two competing companies.

Five current and former LQTS genetic researchers/clinicians we spoke to do not have any current and direct financial conflicts of interest related to genetic testing for variants in the five major genes predisposing to congenital LQTS. We asked them specifically to disclose any financial arrangements linked to LQTS patents and licensees. These experts offered their perspectives on the perceived quality of and/or rationale behind FAMILION testing for LQTS mutations circa 2008:

- Dr. Silvia Priori: "[M]y interpretation of the situation [is] that the company [PGxHealth] is definitely better than any research laboratory. It has to be better than any research laboratory in handling the samples and quickly performing the sequence analysis. Obviously the difference comes in the interpretation of the mutation . . . a research laboratory has a lot of time dedicated to studying the individual mutation. So if I have a patient with a new mutation I am also in the position of being the clinician taking care of that patient . . . I have told [PGxHealth] that I feel quite uncomfortable with the fact that they have been working with very limited input from the scientific community. They seem to be a company consulting with [only] one physician . . . it is clear that [he] is skilled and competent but it is still only one [physician who] is being consulted" (S. Priori, personal communication, 2008). (Dr. Reed notes that Clinical Data held a 19-member advisory board meeting in January 2008 and held a "similarly large" adult electrophysiologist advisory board meeting in the fall of 2008 [C. Reed, personal communication, 2008].)
- Dr. Arthur J. Moss: "[PGxHealth has] more expensive equipment. They do a pretty good job in terms of turnaround [time], but BRLI would do the same thing . . . we have seen a moderate amount of inconsistency and errors. We have had several occasions where PGxHealth was wrong . . ." (Dr. Carol Reed says that she knows of only a single instance and adds that "without specific feedback from our customers, we cannot make test improvements if needed" [C. Reed, personal communication, 2008].) Dr. Moss: "One [error] occurred—off the top of my head—in a test that was run by Jeff Towbin. The physician sent a blood sample [to him and to] FAMILION and the results were different. We tracked this down and repeated the test here. We got the same result as Dr. Towbin and reported this to FAMILION and to the patient. I don't think [the error rate] is large" (A. Moss, personal communication, 2008). (Dr. Moss consulted with Genaissance when that firm held the license to LQTS IP. According to Dr. Moss, Dr. Grodman, CEO of BRLI, wanted to establish a consulting relationship; Dr. Moss declined and instead asked that Dr. Grodman direct funds to the University of Rochester, which it did.) "Complete [genetic] testing of other genes is not really necessary. LQT7 through LQT11 are based on one or two families each, or else based on neurological symptoms where the diagnosis is not very difficult. The Andersen-Tawil syndrome diagnosis is easy to make because of morphological changes in the jaw and face . . . Timothy syndrome is rare and those people [with the syndrome] have striking skeletal defects. Genetic testing is not critical [in those cases] . . ." (A. Moss, personal communication, 2008).
- Dr. Charles Antzelevitch: "We repeated genetic analysis of the same genes screened by FAMILION in only three patients using CLIA-approved methods and found an error in two of the three; the two were members of the same family. In this case FAMILION missed detection of a G insertion in exon 12 of *KCNH2*, causing a frameshift and leading to a stop codon." "[M]y personal view is that FAMILION is filling an important need and is doing a decent job of it, but that it is not in the best interest of science or medicine for any company to a have an absolute monopoly on genetic screening of LQTS. A little friendly competition may improve quality control and reduce prices, thus making it more affordable for all. This would facilitate the acquisition of additional data on genotype-phenotype correlation, thus leading to improved diagnosis, prognosis and a better approach to therapy of LQTS" (C. Antzelevitch, personal communication, 2008).
- Dr. Jeffrey Towbin: "I think it would be valuable for PGxHealth to publish its data . . . [But to] make a genotype-phenotype correlation you have to have the [phenotypic information]. FAMILION can't be expected to have that. I think that while their datasets would be extraordinarily useful if they had the clinical information necessary, I think that's a pipedream the way it's set up now" (J. Towbin, personal communication, 2008). "I have no [real] way of knowing FAMILION′s quality. When you send a sample and you get a result you have no way of knowing unless you run parallel samples. Yes there have been discrepancies on occasion that we've seen. But I don't know who's right; I [might] argue that our laboratories are wrong—we all make mistakes. We don't get the right answer sometimes . . .. On balance, I would say the approach they're taking is reasonable . . .. They've been doing it long enough . . .. I think their system and their thought process make sense. They've done a good job and for some patients have done a real service. The research laboratories were never going to do that. I think [commercial testing is] a useful resource and I think [PGxHealth is] doing it pretty well . . .. If you want a CLIA-approved test for LQTS looking at the standard five genes, it's a very good option . . .. I think Art [Moss] is correct that there have been errors, but no one will meet the perfection standard. [PGxHealth is] good or very good . . .. I think they provide a useful service. Could it be better? Yes. [But] I don't look at them as the bad guy. They're in business, they have standards for quality and turnaround time. That is the state of the art at the moment . . ." (J. Towbin, personal communication, 2008). "[LQTS] is not going to get easier to understand. I don't think we should expect clinicians to understand exactly the meaning of what we're telling people [about their results] . . .. It's very hard in the early 21st century for the average clinician to know enough about genetics to really utilize a [genetic] test. But it's the sexy thing to do" (J. Towbin, personal communication, 2008).
- Dr. Hugh Rienhoff: "[Dr. Towbin's comments are] absolutely true and one of the reasons that the inventor, Dr. Keating, was so willing to 'unload' the responsibility of LQTS testing to DNA Sciences. He did not have a CLIA laboratory, there were no rigorous [standard operating procedures] for testing, no dedicated personnel, [no dedicated] space or devices for the work, and no way to charge for the work. It was regarded as a burden to his laboratory because it used up valuable technician [and] student time and resources. This is a very common set of circumstances in an academic laboratory that has made a discovery and has a unique set of reagents or capabilities" (H. Rienhoff, personal communication, 2008).

Dr. Rienhoff, a clinical geneticist and founder of DNA Sciences, elaborated further on the formidable challenge in interpreting the meaning of genetic variants in diseases such as LQTS:

"This is a problem that is widespread and not specific to the particular parties at hand. New missense mutations will always pose a problem for interpretation. It is a challenge to show that any new variant in a gene has functional consequences [for] either mRNA stability or protein structure and function. It is unrealistic to think anyone could easily resolve the un-interpretability of these findings. Indeed, it simply underscores the fact that we are still early in our description of the human genome and the variants that can be found in it." (H. Rienhoff, personal communication, 2008).

In addition to the difficulty of finding experts who do not have a current or past conflict of interest, another impediment to making objective assessments regarding quality is the present inadequacy of CLIA oversight of genetic testing laboratories.[110,111] The Centers for Medicare and Medicaid Services have yet to institute specific requirements for molecular or biochemical genetic testing laboratories. Thus, although CLIA requires laboratories to have quality assurance programs in place, most genetic testing laboratories are not required by CLIA to perform proficiency testing with specific benchmarks.[111] Moreover, petitions to Centers for Medicare and Medicaid Services to issue updated standards for genetic testing laboratories, including standards for proficiency testing, have thus far gone unheeded.[112] To its credit, PGxHealth has instituted its own proficiency testing program in conjunction with Dr. Ackerman (M. Ackerman and C. Reed, personal communication, 2008). However, when such proficiency testing is in place, there is no CLIA guidance about whether the conduct of such testing under auspices of a paid consultant is an acceptable practice. Clinical Data has opposed more stringent regulation of laboratory-developed tests such as FAMILION.[113]

Allelic dropout is another issue that pertains to test quality. Allelic dropout is a technical problem in DNA amplification,[114] which likely contributed to the relatively low yield of LQTS mutations in the pre-Genaissance/PGxHealth era. A year after commercial launch, at a national meeting, the company presented its experiences with discovery and avoidance of the allelic dropout problems present in assays used by research laboratories.[86] In late 2005, scientists from the Mayo Clinic and what was then still Genaissance submitted an article on the allelic dropout phenomenon to a peer reviewed journal, which appeared in 2006.[77] The recognition of allelic dropout ultimately improved the sensitivity of the test.

As for sample type, PGxHealth Chief Medical Officer Dr. Carol Reed told us via e-mail that, "Our laboratory does and has always accepted paraffin-embedded tissue for testing, so long as it meets quality specifications" (C. Reed, personal communication, 2008). Obtaining DNA from paraffin-embedded tissue can be challenging, however, because the DNA tends to be degraded. According to a recent article from Dr. Ackerman's group, for example, DNA from such tissue should be considered "error prone and unreliable in comprehensive surveillance of sudden unexplained death-associated genes".[115(p. 391)] However, some relatively successful protocols appear to exist, particularly for subsequent amplification of shorter DNA fragments,[116–119] although this may not be practical for all exons in LQTS susceptibility genes (C. Reed and B. Salisbury, personal communication, 2008). Nevertheless, as Dr. Ackerman's group has recommended, given the shortcomings associated with DNA extraction from paraffin-embedded tissue, standard autopsy procedures for sudden unexplained death should include archiving preserved blood or frozen tissue to facilitate postmortem genetic testing.[115]

Adoption by clinical providers

We suspect that relatively few LQTS genetic tests were performed before 2004. GeneDx President Sherri Bale told us that over the course of 2001–2002, her firm ran "about 20" tests (S. Bale, personal communication, 2008). In 2002–2003, Dr. Milunsky's laboratory did 42 (A. Milunsky, personal communication, 2008). After its May 2004 launch, clinical embrace of FAMILION testing started somewhat slowly but has grown substantially in the last 5 years. Extrapolating from Genaissance and Clinical Data filings with the Securities and Exchange Commission, FAMILION LQTS test demand will have increased nearly 10-fold from its launch in 2004 through Clinical Data's fiscal 2009 (ending 31 March, 2009). Genaissance reported FAMILION revenues of $841,000 from the May 2004 launch through June 30, 2005.[102,103] If we assume that, as Clinical Data has during investor presentations,[120] ~85.7% of the revenue derived from FAMILION LQTS tests are from initial $5,400 tests and the remainder is from $900 confirmatory tests of other family members, then approximately 133 initial and 133 confirmatory tests were run in the first 14 months of FAMILION availability. More recently, FAMILION sales grew from ~$2.7 million in fiscal 2007 to ~$4.5 million in fiscal 2008. In the first two quarters of fiscal 2009, FAMILION generated an estimated $4.1 million.[104]

In 2006 clinical guidelines published by the American College of Cardiology, the American Heart Association, and the European Society of Cardiology,[51] genetic testing for LQTS was deemed "very important" for identifying all affected members within a family. In patients affected by LQTS, genetic analysis was considered "useful for risk stratification and for making therapeutic decisions." In an interview with us, Dr. Towbin thought the 2006 guidelines were somewhat inadequate given how new and poorly understood genetic testing was when those guidelines were written; he noted that the Heart Rhythm Society is preparing new guidelines (J. Towbin, personal communication, 2008).

There is ample room for further growth in genetic testing for LQTS. In a January 2007 presentation to investors made by Clinical Data,[120] the company estimated there to be a $94.5-million market for initial LQTS genetic screening ($81 million) and subsequent mutation screening within families ($13.5 million).

Consumer utilization

We can only speculate about whether the patent enforcement actions of the early 2000s adversely affected consumer access to commercial genetic testing for LQTS. The overall number of LQTS patients affected by the patent enforcement actions was probably small. According to Dr. Towbin, there was minimal awareness of genetic testing and poor understanding of LQTS genetics at the time. "In 2002, nobody took DNA Sciences or anyone else seriously as purveyors of a LQTS diagnostic test, in part because they themselves didn't. They weren't advertising, they didn't have buy-in, and [they] were talking about testing for specific mutations, which didn't make sense" (J. Towbin, personal communication, 2008).

PGxHealth does not offer prenatal diagnosis, thereby rendering it commercially unavailable in the United States through 2008. When asked about the subject, PGxHealth's Drs. Reed and Salisbury cited "technical concerns" and "very little demand" given the treatable nature of LQTS. They said that although the company does not have an official policy regarding

prenatal diagnosis, Drs. Reed and Salisbury's advice to the company would be "not to enforce the patent" for such uses (C. Reed and B. Salisbury, personal communication, 2008). GeneDx did offer prenatal testing for LQTS in 2002; however, it was offered only in cases where another family member was known to carry a mutation (Appendix 8; S. Bale, personal communication, 2008). In separate interviews, Drs. Moss and Antzelevitch (MMRL) cautioned us not to overstate the importance of prenatal diagnosis. Both researchers said that prenatal diagnosis would be of limited usefulness given the highly variable phenotype: an infant may harbor a mutation and go on to live a long and healthy life. Dr. Milunsky views the situation differently. He told us that: (1) some families are indeed interested in prenatal diagnosis; (2) distinguishing fetal from maternal DNA is a trivial technical issue that all prenatal diagnostic laboratories must contend with; (3) Clinical Data will not perform prenatal diagnosis; and (4) company representatives made it clear that Clinical Data will not permit his (Milunsky's) laboratory to perform it under any circumstances (A. Milunsky, personal communication, 2008). Dr. Bale (now a competitor to PGxHealth) agrees with Dr. Milunsky that families are interested in prenatal diagnosis and that distinguishing maternal from fetal DNA is not a major technical barrier (S. Bale, personal communication, 2008). Consumers pay different prices for FAMILION testing based on what fraction of the $5400 cost of the test is covered by insurance. Research laboratories charge nothing; however, it may take many months or even years before patients receive their results from research laboratories (A. Moss and S. Priori, personal communication, 2008). In some cases, patients may never receive their results, and the quality may be substandard (J. Towbin, personal communication, 2008). Indeed, non-CLIA-certified laboratories are restricted by law from providing results of testing to the patient or referring physician.[121–124]

Our own informal collation of consumer views of LQTS testing culled from the online C.A.R.E. Cardiac Arrhythmias Support Community (http://www.inspire.com/groups/care-cardiac-arrhythmias/) suggests that LQTS patients want information about their condition, including genetic information. Many are understandably frightened by the prospect of sudden cardiac death and are concerned about potential triggers for such events. As far as we can tell, out-of-pocket cost is the most significant deterrent to consumer utilization, although several patients complained about the turnaround time and the time necessary to negotiate insurance coverage. A summary of our very preliminary findings from the C.A.R.E. forum appears below. It is important to note the caveats: all data are self-reported, and the sample size is minimal. This is a convenience sample of motivated forum participants, not a representative sample of the general population. We take up the payment issue in the next section on adoption by third-party payers. Tables 1–6 provide the C.A.R.E. LQTS genetic testing data.

The lone study that modeled the cost-effectiveness of genetic testing for LQTS concluded that it is indeed cost-effective when compared with no testing.[109] It should be noted that, however, some funding for this 2005 study was provided by Genaissance through independent consulting contracts to two coauthors, Drs. Phillips and Ackerman.[109] Through 2008, there was no systematic study of either clinicians' or payers' considerations of cost as part of their LQTS diagnostic heuristics.

The insurance and employment provisions of the Genetic Information Nondiscrimination Act of 2008 will take effect in 2009 and 2010. This may affect utilization of genetic testing.[125]

Table 1 When was your test performed?

Year	Number
2000	1
2006	1
2007	8
2008	3
Unknown	5

Table 2 Who performed the test?

Laboratory	Number
PGxHealth	12
Research Laboratory	1
Ex-US (PGxHealth)	2 (Canada)
Unknown	3

Table 3 How long did it take for you to receive your results?

	Laboratory			
Time	PGxHealth	Research Laboratory	Ex-US (PGxHealth)	Unknown
				7
3 wk (confirmation testing for additional family members)	2			
4 wk	1			
5 wk	1			
6 wk	2		1	
7 wk	1			
8 wk	1			
9 wk	2		1	
2 yr		1		

Adoption by third party payers

According to the PGxHealth Web site, there were 10 commercial payers with coverage policies supportive of FAMILION testing as of August 2008. These were Aetna, Harvard Pilgrim, BCBS in 16 states (AK, AL, AR, HI, ID, IL, MI, MS, NJ, NM, NY, OK, SD, TN, TX, and WA), Cigna, Coventry Health Care, HIP Plan of NY, Health Net, Inc., Humana, Select Health, and Tufts Health. Among government payers with favorable coverage policies, on its Web site, PGxHealth cited: (1) TRICARE, which is the Department of Defense's health care program for members of the uniformed services, their families, and survivors; and (2) Medicaid in 38 states and the District of Columbia

(the company has applied for Medicaid coverage in all the states of United States and territorial Medicaid jurisdictions). FAMILION testing was not covered by New York State Medicaid until the spring of 2008. Coverage followed a segment on *Good Morning America* highlighting the gap in coverage and its potentially adverse effect on a young LQTS patient of Dr. Chung's.[126] In October 2008, PGxHealth announced that it had become an in-network provider for Aetna's health care coverage of FAMILION tests.[127]

Former Genaissance CSO Dr. Richard Judson told us that, at least initially, "Medicaid's reimbursement rate was so low that it would not begin to cover the cost of the test. It was unfortunate. This is a disease typically diagnosed in childhood and there are lots of children on Medicaid" (R. Judson, personal communication, 2008). Dr. Milunsky's laboratory did accept Medicaid, although he called Medicaid payments "pathetic" (A. Milunsky, personal communication, 2008).

Each of the patent licensees emphasized the difficulty in gaining payer acceptance of the test. At the time of the sale of DNA Sciences' assets to Genaissance, DNA Sciences was negotiating with several private insurers. This process included assembly of a 100- to 150-page package that was meant to justify the cost of the test to potential payers (S. Lehrer, personal communication, 2008). Dr. Judson said the bar was higher for new, complex tests. "Because there are hundreds of individual insurance companies in the United States, novel tests can require hundreds of individualized cases to be made for initial acceptance. The more complex a test is (and hence the more expensive), the longer it takes for acceptance" (R. Judson, personal communication, 2008). In his letter to Congressman Berman, Clinical Data CEO Drew Fromkin said that anyone providing diagnostic services knows that ". . . health insurer coverage for laboratory tests is a long and difficult road and it takes many years for any novel test to gain significant coverage."[23] According to Clinical Data, between January and October 2008, FAMILION payer coverage increased from 55–155 million lives, including Medicaid coverage increasing from 7–37 states during the same period.[127] By early 2010, according to the PGxHealth website, coverage for FAMILION tests had reached 280 million lives.

The clinicians and researchers we interviewed all said they try to make testing available to those who cannot afford it. Dr. Ackerman described a "gentleman's agreement" with PGxHealth whereby if an insurer denies payment, he will offer a charity waiver (M. Ackerman, personal communication, 2008). Dr. Priori provides free testing to patients from developing countries (S. Priori, personal communication, 2008). Drs. Moss and Antzelevitch will enroll patients in research studies (Drs. Arthur Moss and Charles Antzelevitch, personal (A. Moss and C. Antzelevitch, personal communication, 2008). Dr. Chung will try multiple strategies, including shopping around for insurance, pooling family resources, and enrolling patients in research studies (W. Chung, personal communication, 2008). It is important to note again that although the research option is free, it is also very likely to mean a lengthy wait for the patient. And, Dr. Towbin worries that in the current fiscal environment, research laboratories will not be able to continue providing complimentary LQTS genetic testing *ad infinitum* (J. Towbin, personal communication, 2008).

SUMMING UP

Genetic testing for LQTS is a complex story that illustrates several features relevant to clinical access to genetic testing in general. Some of the complexity is biological: the clinical syndrome is uncommon but not rare. The mutations causing it are found in a multitude of genes. Sequencing the five genes most commonly mutated accounts for an estimated 75% of cases, but beyond those, there are many variants that truly are rare.

Table 4 Was a mutation found?

	Laboratory			
	PGxHealth	Research Laboratory	Ex-US (PGxHealth)	Unknown
				8
Yes	5			
No	2	1	1	
Class III variant (not expected to be deleterious)	1			

Table 6 Was cost a factor in your decision to get tested (or not get tested) with FAMILION?

No	7
Yes	6
No answer/not clear	5

Table 5 Who was your insurance carrier and what was your out-of-pocket expense for FAMILION testing (FAMILION testing for LQTS costs $5400 for the index case and $900 to confirm the presence of a mutation in each family member)?

Percent coverage	Insurer Blue Cross/Blue Shield	Humana	TriCare (US Military)	Canadian Provincial	Unknown
100	2		1	2	3
90	1				
80					1
63					1
Unknown partial fraction	1	1			
0%	1				1

The IP overlay of this biological story is also complex. It started with aggregation of the three initial patents by a single firm that "cleared the market" of testing services offering partial LQTS testing, but went bankrupt before it offered a test itself. Its rights were acquired by a second firm that introduced FAMILION, which was in turn sold to Clinical Data, Inc., which continues to offer it through its subsidiary, PGxHealth. This was the main provider of testing in the United States through 2009, although some research laboratories did and do offer testing for indigent patients, for those with rare variants not found by commercial testing, and perhaps in other circumstances.

BRLI has quietly accumulated some exclusive patent rights of its own and has used them strategically to change the market dynamics of LQTS testing. This case shows both how exclusive licensing can enable a single provider to "own" genetic testing for an entire clinical syndrome by holding rights to the most common patented variants and leveraging those rights to cover unpatented variants and variants never before discovered. However, it also illustrates the vulnerability of this strategy to a competitor that acquires countervailing exclusive rights. That was the situation that was unfolding for LQTS testing as this case study was being prepared.

The case also illustrates the fact that coverage decisions by insurers and health plans, and the level of reimbursement payments are arguably larger and more pervasive problems for clinical access to genetic testing than patent status. On the other hand, exclusive patent rights also seem to have contributed to relatively high pricing for LQTS testing.

In some ways, this case is simpler than others that could follow. Most of the key patents were licensed by a single institution, the University of Utah, which has now exclusively licensed rights to different mutations to two different firms. If there were multiple patent holders, then even more parties, with potentially different stakes, would be involved in the negotiations.

The case illustrates how complex and pervasive the financial connections are. The community of clinical experts is fairly small, and its members respect one another's clinical expertise. They disagree about best practices, particularly regarding exclusive licensing of university-based patents involved in genetic testing, and their positions do map to their financial arrangements (although causality could be in both directions—those most trusting of a company's practices are apt to consult for it). Those without financial ties acknowledge the value of commercial testing but also worry about high prices limiting access and the importance of having alternative sources because even high-quality laboratories make mistakes, and the system needs to have checks and balances. We find no consensus among the clinical experts most familiar with the medical consequences of testing, dominated until very recently by a single-provider commercial model, whether the single-provider model is a net social benefit or a problem.

Finally, the case study shows the technological instability of current protocols for genetic testing. If full-genome sequencing becomes feasible in the next few years, and if its price comes into the same range as the $5400 FAMILION test, as seems likely, then the IP consequences will become even more complex. The question of patent infringement will turn on the precise language of relevant patents, how courts interpret those claims, and the business decisions of patent holders with claims on DNA sequences and their clinical interpretation. The choice of total genomic sequencing could be either an alternative to testing for a particular syndrome or full-genome sequencing could become the first step in a clinical decision tree that reduces the role of boutique genetic testing to confirming mutations provisionally detected. This would be a profound perturbation of the current business models. Moreover, genome sequencing will almost certainly lead to a dramatic increase in the number of reported variants in cardiac ion-channel genes that are deemed to be "of unknown significance." This is likely to exacerbate existing problems of variant interpretation by orders of magnitude.

The future promises to add further layers of uncertainty regarding both IP and technological options for genetic testing.

LQTS Case Study Update: November 2009

- In 2008, BRLI obtained exclusive licensing rights from the University of Utah that gave it rights to test for LQT3, which accounts for ~10–15% of inherited LQTS. BRLI also aggregated IP related to susceptibility genes for LQT1, LQT2, LQT5, LQT6, LQT7, and JLNS. As a consequence, the patent landscape for LQTS testing became fragmented between two different exclusive licensees.
- In early 2009, BRLI, via its GeneDx subsidiary, entered the LQTS testing market.[128] It now competes with the previous licensee, Clinical Data, Inc., subsidiary PGxHealth. As of November 2009, GeneDx tested for 10 LQTS susceptibility genes (LQT1 through LQT10),[129] whereas PGxHealth tested for 11 susceptibility genes (LQT1 through LQT3; LQT5 through LQT12).[130] Before 2009, the sole commercial offering, PGxHealth's FAMILION panel, incorporated five genes. It seems reasonable to infer that GeneDx's entry into the market prompted PGxHealth to expand its panel.
- According to GeneDx President and Clinical Director Sherri Bale, the current price for GeneDx's full 10-gene LQTS panel is $2500 for index cases and $350 for confirmatory testing of known mutations (S. Bale, personal communication, 2009). BRLI's 2009 SEC filings through 10 November 2009 make no mention of GeneDx's foray into LQTS testing.[131] Based on a phone call to PGxHealth's toll-free number (877-274-9432) on 9 November 2009, the new FAMILION panel remains $5400 for index cases and $900 for confirmatory testing. Clinical Data's results for the second fiscal quarter that ended September 30, 2009, saw a 51% increase in FAMILION genetic testing gross revenue and a year-over-year increase in gross margins from 36–47%.[132] Neither GeneDx nor PGxHealth advertises its price on its Web site.
- Similar to PGxHealth, GeneDx does not currently offer prenatal genetic testing for LQTS. According Dr. Bale, however, "Technically we could . . . and I might consider it, if I [were] sure that the patient had been counseled appropriately by a genetic counselor. It would be unusual for someone to ask, however, unless [she] had lost a child from LQTS [at] a very young age. And since it is treatable, it is highly unlikely that I will ever be asked, as postnatal diagnosis is going to be just as useful, and less costly and risky. I can't imagine someone would terminate if [she found out a fetus were] affected, so the only real reason to do the test prenatally [would be] if there was something that could be done, treatment wise, in the neonatal period" (S. Bale, personal communication, 2009).

- In fall 2009, PGxHealth scientists and Mayo Clinic investigators published two articles describing variants in large numbers of LQTS patients and family members. In one article, the authors conducted a retrospective analysis of the first 2500 cases to undergo the five-gene version of FAMILION testing. This publication increased the publicly available compendium of LQTS mutations by >50%. Mutation yield was 36%; 9% of mutation-positive cases were compound heterozygotes; and one third of newly detected mutations were found to be novel.[133] In the second article, the investigators compared type, frequency, and location of mutations among 388 clinically confirmed LQTS cases and >1300 controls. Variant type, location, and patient ethnicity were each found to play a role in whether a given variant was likely to be pathogenic.[134]
- These two studies point up the ongoing difficulty in distinguishing benign variants from pathogenic ones, particularly in the absence of phenotypic data.[135] Darbar[136] has advocated a multifaceted approach: (1) screening large, ethnically matched control populations to establish variant frequencies; (2) examining cosegregation of disease and variants in extended pedigrees; (3) examining whether variants are conserved across species; (4) noting mutation type and location; and (5) carrying out functional studies of suspected pathogenic variants. If cardiologists can pool detailed phenotypic data from suspected cases, our hope is that having two commercial entities offering genetic testing for LQTS to whoever needs it and then sharing their findings will enable the development of more reliable correlations between genotype and risk of sudden cardiac death.

ACKNOWLEDGMENTS

All interviews were conducted under Duke University IRB-approved protocol 1277 and usually conducted by phone and recorded. All interviews were covered by an NIH certificate of confidentiality. Researchers obtained informed consent from subjects.

This case study was performed under Grant P50 003391, co-funded by the National Human Genome Research Institute and US Department of Energy, and supplemented by funding from The Duke Endowment. The case study authors have no consultancies, stock ownership, grants, or equity interests that would create financial conflicts of interest. The Center for Genome Ethics, Law and Policy accepts no industry funding. Dr. Robert Cook-Deegan is listed on the British Medical Journal roster of physicians who have pledged to remain independent of industry funding (http://www.tseed.com/pdfs/bmj.pdf); more details about how the case studies were done are noted in a July 29, 2009, letter to the Secretary's Advisory Committee on Genetics, Health, and Society (http://www.genome.duke.edu/centers/gelp/documents/SACGHSResponsetopubliccomments.pdf).

The case study was reviewed by Michael Ackerman, Charles Antzelevitch, Sherri Bale, Wendy Chung, Mary Jo Gordon, Marc Grodman, Richard Judson, Steven Lehrer, Arthur Moss, Silvia Priori, Carol Reed, Hugh Rienhoff, Benjamin Salisbury, Jeffrey Towbin, David Urso, and Raymond Woosley for the Secretary's Advisory Committee on Genetics, Health and Society. The authors thank the experts who provided interviews.

REFERENCES

1. Goldenberg I, Moss AJ. Long QT syndrome. *J Am Coll Cardiol* 2008;51:2291–2300.
2. Roden DM. Clinical practice. Long-QT syndrome. *N Engl J Med* 2008;358:169–176.
3. Goldenberg I, Moss AJ, Peterson DR, et al. Risk factors for aborted cardiac arrest and sudden cardiac death in children with the congenital long-QT syndrome. *Circulation* 2008;117:2184–2191.
4. Berul CI. Congenital long-QT syndromes: who's at risk for sudden cardiac death? *Circulation* 2008;117:2178–2180.
5. Tester DJ, Ackerman MJ. Sudden infant death syndrome: how significant are the cardiac channelopathies? *Cardiovasc Res* 2005;67:388–396.
6. Ackerman MJ. Cardiac channelopathies: it's in the genes. *Nat Med* 2004;10:463–464.
7. Moss AJ, Zareba W, Hall WJ, et al. Effectiveness and limitations of beta-blocker therapy in congenital long-QT syndrome. *Circulation* 2000;101:616–623.
8. Choi GR, Porter CB, Ackerman MJ. Sudden cardiac death and channelopathies: a review of implantable defibrillator therapy. *Pediatr Clin North Am* 2004;51:1289–1303.
9. Passman R, Kadish A. Sudden death prevention with implantable devices. *Circulation* 2007;116:561–571.
10. Zareba W, Moss AJ, Daubert JP, Hall WJ, Robinson JL, Andrews M. Implantable cardioverter defibrillator in high-risk long QT syndrome patients. *J Cardiovasc Electrophysiol* 2003;14:337–341.
11. Wang LX. Role of left cardiac sympathetic denervation in the management of congenital long QT syndrome. *J Postgrad Med* 2003;49:179–181.
12. Curran ME, Splawski I, Timothy KW, Vincent GM, Green ED, Keating MT. A molecular basis for cardiac arrhythmia: HERG mutations cause long QT syndrome. *Cell* 1995;80:795–803.
13. Wang Q, Shen J, Li Z, et al. Cardiac sodium channel mutations in patients with long QT syndrome, an inherited cardiac arrhythmia. *Hum Mol Genet* 1995;4:1603–1607.
14. Wang Q, Shen J, Splawski I, et al. SCN5A mutations associated with an inherited cardiac arrhythmia, long QT syndrome. *Cell* 1995;80:805–811.
15. Wang Q, Curran ME, Splawski I, et al. Positional cloning of a novel potassium channel gene: KVLQT1 mutations cause cardiac arrhythmias. *Nat Genet* 1996;12:17–23.
16. Marban E. Cardiac channelopathies. *Nature* 2002;415:213–218.
17. Lehnart SE, Ackerman MJ, Benson DW Jr, et al. Inherited arrhythmias: a National Heart, Lung, and Blood Institute and Office of Rare Diseases workshop consensus report about the diagnosis, phenotyping, molecular mechanisms, and therapeutic approaches for primary cardiomyopathies of gene mutations affecting ion channel function. *Circulation* 2007;116:2325–2345.
18. Ueda K, Valdivia C, Medeiros-Domingo A, et al. Syntrophin mutation associated with long QT syndrome through activation of the nNOS-SCN5A macromolecular complex. *Proc Natl Acad Sci U S A* 2008;105:9355–9360.
19. Genaissance Pharmaceuticals. EX-99.1 of 8-K, May 11, 2004. Available at: http://www.sec.gov/Archives/edgar/data/1110009/000110465904013687/a04-5741_1ex99d1.htm. Accessed September 26, 2008.
20. Statement of Marc Grodman at stifling or stimulating—the role of gene patents in research and genetic testing. House Judiciary Subcommittee on Courts, the Internet, and Intellectual Property. Washington, DC; 2007. Available at: http://judiciary.house.gov/hearings/pdf/Grodman071030.pdf. Accessed March 2, 2010.
21. Stifling or stimulating: the role of gene patents in research and genetic testing. Subcommittee on Courts, the Internet, and Intellectual Property of the Committee on the Judiciary. One Hundred Tenth Congress; First Session. Washington, DC; October 30, 2007.
22. Written statement of Wendy Chung at stifling or stimulating—the role of gene patents in research and genetic testing. House Judiciary Subcommittee on Courts, the Internet, and Intellectual Property. Washington, DC; 2007. Available at: http://judiciary.house.gov/hearings/pdf/Grodman071030.pdf. Accessed March 2, 2010.
23. Fromkin AJ. Letter to the Honorable Howard L. Berman from Clinical Data CEO Andrew J Fromkin. In: Howard LB, The house judiciary subcommittee on courts, the internet and intellectual property. Washington, DC; April 1, 2008.
24. Ebersole T, Guthrie M, Goldstein JA. Patent pools as a solution to the licensing problems of diagnostic genetics. *IP Technol Law J* 2005;17:6–13.
25. Ebersole TJ, Guthrie MC, Goldstein JA. Patent pools and standard setting in diagnostic genetics. *Nat Biotechnol* 2005;23:937–938.
26. Goldstein J, Golod E. Human gene patents. *Acad Med* 2002;77(12 Part 2):1315–1328.
27. Moss AJ, Schwartz PJ. 25th anniversary of the International Long-QT Syndrome Registry: an ongoing quest to uncover the secrets of long-QT syndrome. *Circulation* 2005;111:1199–1201.
28. John Welsh Cardiovascular Diagnostic Laboratory. Panels offered by dis-

ease, 2009. Available at: http://www.bcm.edu/pediatrics/index.cfm?Realm=99992426&This_Template=Genetic_Testing. Accessed November 19, 2008.
29. Boettiger S, Bennett AB. Bayh-Dole: if we knew then what we know now. *Nat Biotechnol* 2006;24:320–323.
30. Thursby JG, Thursby MC. Intellectual property. University licensing and the Bayh-Dole Act. *Science* 2003;301:1052.
31. Genaissance Pharmaceuticals to merge with Clinical Data. *Pharmacogenomics* 2005;6:459.
32. DNA Sciences. S-1, January 5, 2001; Available at: http://www.sec.gov/Archives/edgar/data/1130013/000091205701000445/a2033717zs-1.htm. Accessed September 22, 2008.
33. Clinical Data. 10-K, 2006. Available at: http://www.sec.gov/Archives/edgar/data/716646/000095013506004150/b61410cie10vk.htm. Accessed November 21, 2009.
34. Genaissance Pharmaceuticals. 10-K, March 30, 2004. Available at: http://www.sec.gov/Archives/edgar/data/1110009/000104746904010049/a2131537z10-k.htm. Accessed September 23, 2008.
35. Genaissance Pharmaceuticals. Genaissance Pharmaceuticals launches its proprietary FAMILION™ test for genetic mutations associated with sudden cardiac death, 2004. Available at: http://www.medscape.com/pages/editorial/pressreleases/pr-crm-genaissance2. Accessed September 17, 2008.
36. Napolitano C, Bloise R, Priori SG. Long QT syndrome and short QT syndrome: how to make correct diagnosis and what about eligibility for sports activity. *J Cardiovasc Med (Hagerstown)* 2006;7:250–256.
37. Napolitano C, Priori SG, Schwartz PJ, et al. Genetic testing in the long QT syndrome: development and validation of an efficient approach to genotyping in clinical practice. *JAMA* 2005;294:2975–2980.
38. Ackerman MJ. Genetic testing for risk stratification in hypertrophic cardiomyopathy and long QT syndrome: fact or fiction? *Curr Opin Cardiol* 2005;20:175–181.
39. Priori SG, Napolitano C, Schwartz PJ. Low penetrance in the long-QT syndrome: clinical impact. *Circulation* 1999;99:529–533.
40. Priori SG, Schwartz PJ, Napolitano C, et al. Risk stratification in the long-QT syndrome. *N Engl J Med* 2003;348:1866–1874.
41. Taggart NW, Haglund CM, Tester DJ, Ackerman MJ. Diagnostic miscues in congenital long-QT syndrome. *Circulation* 2007;115:2613–2620.
42. Tan HL, Bardai A, Shimizu W, et al. Genotype-specific onset of arrhythmias in congenital long-QT syndrome: possible therapy implications. *Circulation* 2006;114:2096–2103.
43. Ackerman MJ. Genotype-phenotype relationships in congenital long QT syndrome. *J Electrocardiol* 2005;38(4 suppl):64–68.
44. Schwartz PJ, Priori SG, Spazzolini C, et al. Genotype-phenotype correlation in the long-QT syndrome: gene-specific triggers for life-threatening arrhythmias. *Circulation* 2001;103:89–95.
45. Wilde AA, Jongbloed RJ, Doevendans PA, et al. Auditory stimuli as a trigger for arrhythmic events differentiate HERG-related (LQTS2) patients from KVLQT1-related patients (LQTS1). *J Am Coll Cardiol* 1999;33:327–332.
46. Seth R, Moss AJ, McNitt S, et al. Long QT syndrome and pregnancy. *J Am Coll Cardiol* 2007;49:1092–1098.
47. Moss AJ, Shimizu W, Wilde AA, et al. Clinical aspects of type-1 long-QT syndrome by location, coding type, and biophysical function of mutations involving the *KCNQ1* gene. *Circulation* 2007;115:2481–2489.
48. Priori SG, Napolitano C, Schwartz PJ, et al. Association of long QT syndrome loci and cardiac events among patients treated with beta-blockers. *JAMA* 2004;292:1341–1344.
49. Ching CK, Tan EC. Congenital long QT syndromes: clinical features, molecular genetics and genetic testing. *Expert Rev Mol Diagn* 2006;6:365–374.
50. Oliva A, Bjerregaard P, Hong K, et al. Clinical heterogeneity in sodium channelopathies. What is the meaning of carrying a genetic mutation? *Cardiology* 2008;110:116–122.
51. Zipes DP, Camm AJ, Borggrefe M, et al. ACC/AHA/ESC 2006 Guidelines for Management of Patients With Ventricular Arrhythmias and the Prevention of Sudden Cardiac Death: a report of the American College of Cardiology/American Heart Association Task Force and the European Society of Cardiology Committee for Practice Guidelines (writing committee to develop Guidelines for Management of Patients With Ventricular Arrhythmias and the Prevention of Sudden Cardiac Death): developed in collaboration with the European Heart Rhythm Association and the Heart Rhythm Society. *Circulation* 2006;114:e385–e484.
52. Sudden Arrhythmia Death Syndromes Foundation. Genetic testing, 2009. Available at: http://www.sads.org/index.php/Table/Genetic-Testing/. Accessed September 15, 2008.
53. Sudden Arrhythmia Death Syndromes Foundation. Annual report, 2005. Available at: http://www.sads.org/images/stories/pdf/newsletter/2005/SADS_Sm_05_Annual_Report.pdf. Accessed November 21, 2009.
54. Hlatky MA, Mark DB. The high cost of implantable defibrillators. *Eur Heart J* 2007;28:388–391.
55. Abbott GW, Sesti F, Splawski I, et al. MiRP1 forms IKr potassium channels with HERG and is associated with cardiac arrhythmia. *Cell* 1999;97:175–187.
56. Larsen LA, Andersen PS, Kanters J, et al. Screening for mutations and polymorphisms in the genes *KCNH2* and *KCNE2* encoding the cardiac HERG/MiRP1 ion channel: implications for acquired and congenital long Q-T syndrome. *Clin Chem* 2001;47:1390–1395.
57. Neyroud N, Richard P, Vignier N, et al. Genomic organization of the *KCNQ1 K+* channel gene and identification of *C*-terminal mutations in the long-QT syndrome. *Circ Res* 1999;84:290–297.
58. Splawski I, Shen J, Timothy KW, Vincent GM, Lehmann MH, Keating MT. Genomic structure of three long QT syndrome genes: *KVLQT1*, *HERG*, and *KCNE1*. *Genomics* 1998;51:86–97.
59. Syrris P, Murray A, Carter ND, McKenna WM, Jeffery S. Mutation detection in long QT syndrome: a comprehensive set of primers and PCR conditions. *J Med Genet* 2001;38:705–710.
60. Tsui LC, Durie P. Genotype and phenotype in cystic fibrosis. *Hosp Pract (Minneap)* 1997;32:115–129.
61. Tester DJ, Salisbury BA, Carr JL, Harris-Kerr C, Reed CR, Ackerman MJ. Clinical phenotype and the yield of the Familion(TM) genetic test for congenital Long QT syndrome. Abstract presented at Heart Rhythm Society Meeting. Denver, CO, May 9–12, 2007.
62. Tester DJ, Salisbury BA, Carr JL, Harris-Kerr C, Reed CR, Ackerman MJ. The effect of mutation class on QTc in unrelated patients referred for the Familion(TM) genetic test for Long QT syndrome. Abstract presented at Heart Rhythm Society Meeting. Denver, CO, May 9–12, 2007.
63. Tester DJ, Will ML, Haglund CM, Ackerman MJ. Effect of clinical phenotype on yield of long QT syndrome genetic testing. *J Am Coll Cardiol* 2006;47:764–768.
64. Centers for Medicare and Medicaid Services. Overview Clinical Laboratory Improvement Amendments (CLIA). Available at: http://www.cms.hhs.gov/clia/. Accessed November 11, 2008.
65. PGxHealth. Patients, 2009. Available at: http://www.pgxhealth.com/familion/patients/. Accessed November 21, 2009.
66. PGxHealth. Patients: frequently asked questions, 2009. Available at: http://www.pgxhealth.com/familion/patients/faq.cfm. Accessed November 21, 2009.
67. Clinical Data. EX-99.1 of 8-K, July 9, 2008. Available at: http://www.sec.gov/Archives/edgar/data/716646/000095013508004859/b71062cdexv99w1.htm. Accessed September 17, 2008.
68. Clinical Data. 10-K, June 16, 2008. Available at: http://www.sec.gov/Archives/edgar/data/716646/000095013508004390/b70423cde10vk.htm. Accessed September 17, 2008.
69. Saenen JB, Vrints CJ. Molecular aspects of the congenital and acquired long QT Syndrome: clinical implications. *J Mol Cell Cardiol* 2008;44:633–646.
70. Schwartz PJ. The congenital long QT syndromes from genotype to phenotype: clinical implications. *J Intern Med* 2006;259:39–47.
71. Wang DW, Yazawa K, George AL Jr, Bennett PB. Characterization of human cardiac Na+ channel mutations in the congenital long QT syndrome. *Proc Natl Acad Sci U S A* 1996;93:13200–13205.
72. Williams-Jones B. History of a gene patent: tracing the development and application of commercial BRCA testing. *Health Law J* 2002;10:123–146.
73. Frank TS, Deffenbaugh AM, Reid JE, et al. Clinical characteristics of individuals with germline mutations in BRCA1 and BRCA2: analysis of 10,000 individuals. *J Clin Oncol* 2002;20:1480–1490.
74. Clinical Data Launches Genetic Test for Arrhythmogenic Right Ventricular Cardiomyopathy (ARVC)—company to release its genetic databases for inherited cardiac conditions. *Business Wire*. November 10, 2008. Available at: http://investor.clda.com/releasedetail.cfm?ReleaseID=346585. Accessed January 27, 2010.
75. Ackerman MJ, Splawski I, Makielski JC, et al. Spectrum and prevalence of cardiac sodium channel variants among black, white, Asian, and Hispanic individuals: implications for arrhythmogenic susceptibility and Brugada/long QT syndrome genetic testing. *Heart Rhythm* 2004;1:600–607.
76. Judson RS, Salisbury BA, Reed CR, Ackerman MJ. Pharmacogenetic issues in thorough QT trials. *Mol Diagn Ther* 2006;10:153–162.
77. Tester DJ, Cronk LB, Carr JL, et al. Allelic dropout in long QT syndrome genetic testing: a possible mechanism underlying false-negative results. *Heart Rhythm* 2006;3:815–821.
78. Salisbury BA, Carr JL, Harris-Kerr C, Ackerman MJ. Abstract 2215: clinical genetic testing for congenital Long QT syndrome: spectrum of mutations discovered in the first two years. Abstract presented at American Heart Association Meeting. November 2006.
79. Tester DJ, Salisbury BA, Carr JL, Harris-Kerr C, Reed CR, Ackerman MJ. Should a minimum corrected QT interval (QTc) be a prerequisite for Long QT syndrome genetic testing? Abstract presented at American Heart Association Meeting. November 6, 2007.
80. Ackerman MJ, Tester DJ, Valdivia C, Salisbury BA, Wilde AAM, Mak-

ielski JC. Is A572-SCN5A a LQT3/sudden death susceptibility mutation or background genetic noise? Abstract presented at Heart Rhythm Society Meeting. San Francisco, CA, May 14–17, 2008.
81. Johnson JN, Haglund CM, Tester DJ, et al. Prevalence of early onset atrial fibrillation in congenital Long QT syndrome. Abstract presented at Heart Rhythm Society Meeting. Denver, CO, May 9–12, 2007.
82. Kapa S, Tester DJ, Salisbury BA, Wilde AA, Ackerman MJ. Distinguishing Long QT Syndrome-causing mutations from "background" genetic noise. Abstract presented at Heart Rhythm Society Meeting. San Francisco, CA, May 16, 2008.
83. Kapa S, Tester DJ, Salisbury BA, Wilde AA, Ackerman MJ. Amino acid physicochemical differences may serve as an adjunct to frequency analysis to determine mutation pathogenicity in Long QT syndrome. Abstract presented at Heart Rhythm Society Meeting. San Francisco, CA, May 15, 2008.
84. Salisbury B, Judson RS, Pungliya M, et al. The single nucleotide polymorphism D85N-KCNE1 is associated with both congenital and drug-induced Long QT. Abstract presented at Heart Rhythm Society Meeting. Boston, MA, May 17–20, 2006.
85. Salisbury BA, Pungliya M, Harris-Kerr C, et al. Distinguishing causative and non-causative mutations in Long QT syndrome. Abstract presented at Heart Rhythm Society Meeting. Boston, MA, May 17, 2006.
86. Tester DJ, Will ML, Salisbury BA, et al. Allelic drop-out in long QT syndrome genetic testing: a possible mechanism underlying false negative results. Abstract presented at Heart Rhythm Society Meeting. New Orleans, LA, May 4–7, 2005.
87. Will ML, Tester DJ, Salisbury BA, et al. Repeat long QT syndrome genetic testing of phenotype positive cases: prevalence and etiology of detection misses. Abstract presented at Heart Rhythm Society Meeting. New Orleans, LA, May 4–7, 2005.
88. Judson RS, Salisbury BA, Pungliya M, et al. A common single nucleotide polymorphism associated with congenital long QT syndrome. Abstract presented at the American Society of Human Genetics Meeting. Salt Lake, UT, October 28, 2005.
89. Pungliya M, Salisbury BA, Judson RS, Tester DJ, Will ML, Ackerman MJ. A comparison of mutation patterns in suspected cases of congenital long QT syndrome and controls. Abstract presented at the American Society of Human Genetics Meeting. Salt Lake, UT, October 28, 2005.
90. Ramsden SC, Deans Z, Robinson DO, et al. Monitoring standards for molecular genetic testing in the United Kingdom, the Netherlands, and Ireland. *Genet Test* 2006;10:147–156.
91. Hertzberg M, Neville S, McDonald D. External quality assurance of molecular analysis of haemochromatosis gene mutations. *J Clin Pathol* 2006;59:744–747.
92. Keating MT, Curran ME, Wang Q; University of Utah Research Foundation, assignee. Long QT syndrome genes. US patent 5,599,673. 4 February, 1997.
93. Keating MT, Sanguinetti MC, Splawski I; University of Utah Research Foundation, assignee. Mutations in the *KCNE1* gene encoding human MINK which cause arrhythmia susceptibility thereby establishing KCNE1 as an *LQT* gene. US patent 6,432,644 B1. August 13, 2002.
94. Keating MT, Splawski I; University of Utah Research Foundation, assignee. Mutations in and genomic structure of *HERG*—a Long QT syndrome gene. US patent 6,207,383 B1. March 27, 2001.
95. Company news—DNA sciences declares bankruptcy, sells assets to Genaissance. *Biotechnol Law Rep* 2003;22:307.
96. Genaissance Pharmaceuticals. Event Transcript: GNSC—Q4 2003 Genaissance Pharmaceuticals, Inc. Earnings Conference Call: CCBN Street Events; 2004.
97. Clinical Data. 10-K, June 29, 2006. Available at: http://www.sec.gov/Archives/edgar/data/716646/000095013506004150/b61410cie10vk.htm. Accessed September 23, 2008.
98. Butkus B. BU Genetics Center stops using Athena Dx tests after firm tightens IP restrictions. *Biotech Transfer Week.* August 20, 2008.
99. Bio-Reference Laboratories, Inc. announces agreement to acquire gene-based testing laboratory, third quarter results and reaffirms guidance for year; company signals major initiative into gene-based testing by acquiring GeneDx. *Business Wire*, August 29, 2006. Available at: http://phx.corporate-ir.net/phoenix.zhtml?c=84759&p=irol-newsArticle_Print&ID=900168&highlight=. Accessed January 27, 2010.
100. Verbeure B, van Zimmeren E, Matthijs G, Van Overwalle G. Patent pools and diagnostic testing. *Trends Biotechnol* 2006;24:115–120.
101. Wang Q, Li Z, Shen J, Keating MT. Genomic organization of the human *SCN5A* gene encoding the cardiac sodium channel. *Genomics* 1996;34:9–16.
102. Genaissance Pharmaceuticals. 10-Q, August 9 2005. Available at: http://www.sec.gov/Archives/edgar/data/1110009/000110465905037531/a05-13057_110q.htm. Accessed September 24, 2008.
103. Genaissance Pharmaceuticals. 10-K, March 15, 2005. http://www.sec.gov/Archives/edgar/data/1110009/000104746905006537/a2152822z10-k.htm. Accessed September 24, 2008.
104. Clinical Data. Clinical Data announces second quarter fiscal 2009 financial results, 2008. Available at: http://www.clda.com/uploads/CLDA_Q2-09%2011-3-08FINAL.pdf. Accessed November 4, 2008.
105. Clinical Data. Clinical Data announces license agreement with Victorian Clin Genet Services Ltd., 2007. Available at: http://www.clda.com/uploads/LQTaustralia-draft%20press%20release10107FINAL.pdf. Accessed October 6, 2008.
106. Hypertrophic Cardiomyopathy Association. Who can conduct genetic testing in HCM? 2008. Available at: http://www.4hcm.org/WCMS/index.php?id=81,0,0,1,0,0. Accessed October 7, 2008.
107. Correlagen Diagnostics Inc. Laboratory receives accreditation from College of American Pathologists, 2007. Available at: http://www.correlagen.com/about/downloads/Correlagen_CAP_NewsRelease_030507.pdf. Accessed November 19, 2008.
108. Tester DJ, Ackerman MJ. Genetic testing for cardiac channelopathies: ten questions regarding clinical considerations for heart rhythm allied professionals. *Heart Rhythm* 2005;2:675–677.
109. Phillips KA, Ackerman MJ, Sakowski J, Berul CI. Cost-effectiveness analysis of genetic testing for familial long QT syndrome in symptomatic index cases. *Heart Rhythm* 2005;2:1294–1300.
110. Hudson KL. Genetic testing oversight. *Science* 2006;313:1853.
111. Report of the Secretary's Advisory Committee on Genetics, Health, and Society. U.S. system of oversight of genetic testing: a response to the charge of the Secretary of Health and Human Services. Bethesda, MD: Secretary's Advisory Committee on Genetics, Health, and Society; 2008.
112. Genetic Alliance. Letter to the Centers for Medicare and Medicaid Services (CMS) requesting a genetics speciality under the CLinical Laboratory Improvement Amendments (CLIA) June 6, 2006. Available at: http://www.geneticalliance.org/policy.clia.letter. Accessed October 7, 2008.
113. Clinical Data, Inc. Reaffirms support for current regulation of laboratory-developed tests. *Business Wire* December 16, 2008. Available at: http://investor.clda.com/releasedetail.cfm?ReleaseID=354524. Accessed January 27, 2010.
114. Johnson PC, Haydon DT. Maximum-likelihood estimation of allelic drop-out and false allele error rates from microsatellite genotypes in the absence of reference data. *Genetics* 2007;175:827–842.
115. Carturan E, Tester DJ, Brost BC, Basso C, Thiene G, Ackerman MJ. Postmortem genetic testing for conventional autopsy-negative sudden unexplained death: an evaluation of different DNA extraction protocols and the feasibility of mutational analysis from archival paraffin-embedded heart tissue. *Am J Clin Pathol* 2008;129:391–397.
116. Dedhia P, Tarale S, Dhongde G, Khadapkar R, Das B. Evaluation of DNA extraction methods and real time PCR optimization on formalin-fixed paraffin-embedded tissues. *Asian Pac J Cancer Prev* 2007;8:55–59.
117. Gillio-Tos A, De Marco L, Fiano V, et al. Efficient DNA extraction from 25-year-old paraffin-embedded tissues: study of 365 samples. *Pathology* 2007;39:345–348.
118. Santos MC, Saito CP, Line SR. Extraction of genomic DNA from paraffin-embedded tissue sections of human fetuses fixed and stored in formalin for long periods. *Pathol Res Pract* 2008;204:633–636.
119. Santos S, Sa D, Bastos E, et al. An efficient protocol for genomic DNA extraction from formalin-fixed paraffin-embedded tissues. *Res Vet Sci* 2009;86:421–426.
120. Clinical Data. EX-99.1 of 8-K, January 18, 2007. Available at: http://www.sec.gov/Archives/edgar/data/716646/000095013507000224/b63771cdexv99w1.htm. Accessed June 6, 2008.
121. Medicare and Medicaid programs; Medicare, Medicaid, and Clinical Laboratories Improvement Act (CLIA) patient confidentiality rules—PHS and HCFA. Final rule. *Fed Regist* 1988;53:48645–48648.
122. Schwartz MK. Genetic testing and the Clinical Laboratory Improvement Amendments of 1988: present and future. *Clin Chem* 1999;45:739–745.
123. Rivers PA, Dobalian A, Germinario FA. A review and analysis of the Clinical Laboratory Improvement Amendment of 1988: compliance plans and enforcement policy. *Health Care Manage Rev* 2005;30:93–102.
124. Bookman EB, Langehorne AA, Eckfeldt JH, et al. Reporting genetic results in research studies: summary and recommendations of an NHLBI working group. *Am J Med Genet A* 2006;140:1033–1040.
125. Slaughter LM. The Genetic Information Nondiscrimination Act: why your personal genetics are still vulnerable to discrimination. *Surg Clin North Am* 2008;88:723–738, vi.
126. Cuomo C, Wagschal G. Lifesaving test held up by paperwork, 2008 Available at: http://abcnews.go.com/GMA/OnCall/story?id=4358619&page=1. Accessed October 22, 2008.
127. Clinical Data, Inc. Signs Contract with Aetna for In-network Coverage of FAMILION® Genetic Tests for Inherited Cardiac Syndromes. *Business Wire*. October 27, 2008. Available at: http://www.businesswire.com/portal/site/home/permalink/?ndmViewId=news_view&newsId=20081027005655&newsLang=en. Accessed January 27, 2010.

128. GeneDx. Genetic testing for hypertrophic cardiomyopathy (HCM), dilated cardiomyopathy (DCM) and Long QT syndrome (LQTS), 2009. Available at: http://www.genedx.com/site/cardiomyopathy_genetic_testing. Accessed November 10, 2009.
129. Test information sheet: cardiology genetics: hypertrophic cardiomyopathy (HCM) panel, October 15, 2009. http://www.genedx.com/ext_upload_files/info_sheet_hcm.pdf. Accessed November 10, 2009.
130. PGxHealth. Familion technical specifications, October 2009. Available at: http://www.pgxhealth.com/familion/pdf/FAMILION_TechSheet%2009TS1008.pdf. Accessed November 10, 2009.
131. Search results for filings from Bio Reference Laboratories Inc. Available at: http://www.sec.gov/cgi-bin/browse-edgar?company=&match=&CIK=BRLI&filenum=&State=&Country=&SIC=&owner=exclude&Find=Find+Companies&action=getcompany. Accessed November 10, 2009.
132. Clinical Data. Clinical Data, Inc. reports second quarter fiscal 2010 results, 2009. Available at: http://investor.clda.com/releasedetail.cfm?ReleaseID=422745. Accessed November 10, 2009.
133. Kapplinger J, Tester D, Salisbury B, et al. Spectrum and prevalence of mutations from the first 2,500 consecutive unrelated patients referred for the FAMILION long QT syndrome genetic test. *Heart Rythm* 2009;6:1297–1303.
134. Kapa S, Tester D, Salisbury B, et al. Genetic testing for long-QT syndrome: distinguishing pathogenic mutations from benign variants. *Circulation* 2009;120:1752–1760.
135. MacRae C. Closer look at genetic testing in long-QT syndrome: will DNA diagnostics ever be enough? *Circulation* 2009;120:1745-1748.
136. Darbar D. Is it time to develop a "pathogenicity" score to distinguish long QT syndrome causing mutations from "background" genetic noise? *Hearth Rythm* 2009;6:1304–1305.

APPENDIX 1

FAMILION®
GENETIC TESTS FOR INHERITED CARDIAC SYNDROMES

Technical Specifications August 2008

The results of these tests should be interpreted and utilized after review of the following specifications:

Indications

These tests are indicated for individuals with suspected Familial Long QT Syndrome (LQTS), Brugada Syndrome (BrS), Catecholaminergic Polymorphic Ventricular Tachycardia (CPVT), Hypertrophic Cardiomyopathy (HCM), and related syndromes, or for family members of individuals who have tested positive for a genetic variant associated with one of these conditions. These tests identify genetic variants in genes in which mutations have been shown to cause or create susceptibility to these syndromes.

Description of Genetic Assays

The *FAMILION* tests include 5 testing options. The first 4 options are index tests, which include comprehensive sequence determination and variant detection in open reading frame and intronic sequences containing splice junction sites for the included exons.

1. LQTS Test. Provides analysis covering all exons (73 amplicons) of five genes associated with LQTS as follows and is indicated for cases of suspected Long QT Syndrome: *KCNQ1* (LQT1), *KCNH2* (LQT2), *SCN5A* (LQT3), *KCNE1* (LQT5), and *KCNE2* (LQT6) and other syndromes attributed to mutations in these genes.

2. BrS Test. Provides analysis covering all exons (34 amplicons) of the gene *SCN5A* (BrS1) and is indicated for cases of suspected Brugada Syndrome and other syndromes attributed to mutations in *SCN5A*.

3. CPVT Test. Provides analysis covering selected exons (41 amplicons) of the gene *RYR2* (CPVT1) and is indicated for cases of suspected Catecholaminergic Polymorphic Ventricular Tachycardia. The following 38 exons are covered, which includes all those in which CPVT-associated mutations have been reported as of April, 2008, and others that are adjacent: 3, 8-15, 37, 41, 44-50, 83, 87-105.

4. HCM Test. Provides analysis covering all exons (113 amplicons) of nine genes associated with HCM as follows and is indicated for cases of suspected Hypertrophic Cardiomyopathy: *ACTC*, *MYBPC3*, *MYH7*, *MYL2*, *MYL3*, *TNNT2*, *TNNI3*, *TNNC1*, and *TPM1*.

5. Family Specific Test. Provides analysis of one or more Class I or II variants (see below) found in an index case and is indicated for testing blood-relatives. Includes sequence determination and variant detection in the gene region(s) in which mutation(s) were detected in the index case for the family. If additional mutations or variants are found in the Family Specific Test, these will also be reported.

Description of Methods

1. Sample acquisition: An 8 ml blood sample in two (2) 4 ml EDTA tubes provided in the sample collection kit is required and shipped overnight at room temperature to the test laboratory. Genomic DNA is isolated from fresh whole blood. Bar codes on each tube provide sample tracking. DNA, frozen blood, and frozen and paraffin-embedded tissue samples are also accepted if they meet specific requirement criteria. Please contact our Customer Service Department to discuss these criteria.

2. DNA Sequence Analysis: DNA amplification by polymerase chain reaction (PCR) is used to generate templates for direct sequencing. A number of PCR amplicons are utilized to obtain coverage of the complete open reading frame, splice junction sites and flanking regions for the targeted regions of each gene. Directed sequencing is performed in both forward and reverse directions using dye-terminator chemistries for all regions except for those regions that, due to constraints within the particular DNA sequence, are amplified twice and then sequenced in a single direction. Automated electrophoretic separation of sequencing reactions is performed.

3. Variant Detection: Sequence traces are analyzed for heterozygous or homozygous variants with respect to public reference sequences that have been confirmed by sequencing hundreds of individuals of diverse ancestry. For each amplicon, the analysis employs reference traces that were generated using the same protocol as the patients' traces. Sequence traces are computationally and visually compared with reference traces to identify and validate variant calls. In order to be analyzed, each trace must meet rigorous quality standards. Two technologists independently score all traces for variants and a supervisor reconciles discrepancies.

4. Report Generation: Class I, II, and III variants, as defined below, are reported. The final report is reviewed and signed by a CLIA licensed Laboratory Director.

Performance Characteristics

1. Analytical Specificity (Index Tests): The chance of a falsely detected genetic variant is minimized by requiring that each variant be seen in independent sequence traces and that two trained technicians independently examine each trace. For each positive finding of a Class I or Class II variant (see definitions below), a second round of PCR amplification and sequencing is performed to confirm the initial finding. Chances of false positives are further minimized by using a validated sample tracking system involving robotics and barcodes.

2. Analytical Sensitivity (Index Tests): Failure to detect a variant in an analyzed amplicon could be due to an amplicon being refractory to analysis by direct DNA sequencing, sample mishandling, sample tracking errors or errors in data analysis. The rate of such errors is estimated to be < 1%.

3. Clinical Sensitivity: It is estimated that detectable variants in these gene panels respectively account for 60-80% of LQTS, 15-30% of Brugada Syndrome, 50-55% of CPVT, and 50-60% of HCM (Tester et al. Heart Rhythm 2:507-517, 2005; Napolitano and Priori. Heart Rhythm 4:675-678, 2007; Taggart et al. Circulation 115:2613-2620, 2007; Keren et al. Nature Clinical Practice Cardiovascular Medicine 5:158-68, 2008.).

4. Clinical Specificity: It is estimated that 5% of apparently unaffected individuals test positive for a possible or probable deleterious mutation in one of the five LQTS genes, approximately 3% in *SCN5A* alone, 3% for CPVT, and a few percent for HCM (Ackerman et al. Mayo Clinic Proceedings 78:1479-1487, 2003; Ackerman et al. Heart Rhythm 1:600-607,

2004; Tester et al. Circulation 112:II-516, 2005). Therefore, comprehensive clinical evaluation is strongly recommended to direct treatment decisions for both positive and negative test results.

5. Family Specific Test: The analytical sensitivity, analytical specificity, and clinical sensitivity of these analyses are all approximately 100%.

6. Limitations: There may be amplicons for which it is not possible to generate traces in both directions. These tests will not detect large DNA rearrangements or deletions and will not detect errors in RNA transcription or processing that are unrelated to coding sequence variants of DNA exons. The tests will not detect mutations in non-targeted exons, nor in exons that belong to alternate transcripts. For many of these syndromes, mutations in other genes have been rarely implicated as causative but are not tested in these analyses.

Variant Classification and Interpretation

DNA variants are identified and classified by comparison with reference sequences and the PGxHealth Variant Database. This database is produced through review of published literature and through results of PGxHealth's sequencing. This database also contains an extensive collection of common polymorphisms and rare variants in these genes that are not expected to confer susceptibility to congenital arrhythmia syndromes; these variants were found in comprehensive scanning of the genes in several hundred individuals of diverse race and ethnicity or from study of the literature, together referred to as the "Reference Panel", which differs in composition across the tested genes. The healthy individuals in the Reference Panel were not known to have inherited cardiac syndromes (Ackerman et al. Mayo Clin Proc 78:1479-1487, 2003; Ackerman et al. Heart Rhythm 1:600-607, 2004). An expert scientist ensures variant classification and interpretation reflect current, published information.

Each variant that is detected is categorized into one of 4 classes. These classes and classification rules are described below. Based on additional evidence, rare exceptions may be made and will be noted in the test report. *Note:* These classes should not be confused with the designations such as LQT1, LQT2, LQT3, etc., which relate to the syndrome and affected gene.

CLASS I: Deleterious and Probable Deleterious Mutations

LQTS and BrS Tests

1. Evidence of deleteriousness
2. Nonsense variant
3. Missense single nucleotide variant not seen in the Reference Panel in transmembrane-spanning domain or pore
4. Insertion or deletion
   a. Frameshift variant
   b. In-frame variant in transmembrane-spanning domain or pore

CPVT and HCM Tests

1. Evidence of deleteriousness
2. Nonsense variant
3. Insertion or deletion causing a frameshift

CLASS II: Possible Deleterious Mutations (Variants of Uncertain Significance)

LQTS and BrS Tests

1. Missense single nucleotide variant not seen in the Reference Panel and not in transmembrane-spanning domain or pore
2. Missense single nucleotide variant seen in the Reference Panel with allelic frequency < 0.5%, but with published evidence of deleteriousness
3. In-frame insertion or deletion not in transmembrane-spanning domain or pore
4. Predicted splice site variant

CPVT and HCM Tests

1. Missense single nucleotide variant not seen in the Reference Panel
2. Missense single nucleotide variant seen in the Reference Panel with allelic frequency < 0.5%, but with published evidence of deleteriousness
3. In-frame insertion or deletion
4. Predicted splice site variant

CLASS III: Polymorphisms (Variants Not Generally Expected to be Deleterious)

1. Protein-altering variant seen in the Reference Panel with either
   a. Common frequency (≥ 0.5%) or
   b. Rare frequency (< 0.5%) and without published evidence of deleteriousness

CLASS IV: Non-Protein-Altering Variants

All non-coding and synonymous variants (no changes in encoded amino acid) except those predicted to affect intron splicing, which are categorized as Class II Mutations (splice variants). These variants do not alter the protein coding sequence. Because of the lack of known or suspected clinical significance, these variants are not reported.

Recommendation for family member testing: In cases where a Class I or Class II mutation is found, a recommendation for clinical evaluation and genetic testing of first-degree blood relatives will be included in the report.

Change of interpretation and amended reports: If there is a change in the clinical interpretation of a reported variant, an amended test report will be generated and provided to the referring physician, when possible. A change in interpretation may be due to new evidence that indicates a variant is more or less likely to be deleterious than indicated by evidence existing at the time of initial reporting.

Laboratory: The *FAMILION* tests are performed by PGxHealth, LLC, 5 Science Park, New Haven, CT 06511. The U.S. Food and Drug Administration (FDA) has not approved these tests; however, FDA approval is not currently required for clinical use of these tests. These tests meet the requirements for high complexity tests under the Clinical Laboratory Improvement Amendments Act and its implementing regulations.

APPENDIX 2

FAMILION®
GENETIC TESTS FOR INHERITED CARDIAC SYNDROMES

LQTS Test Report
(CONFIDENTIAL)

PHYSICIAN	SPECIMEN	PATIENT
Physician's Name:	Specimen Type: Blood	Patient's Name:
Hospital/Institution:	Draw Date:	Date of Birth:
Mailing Address:	Receive Date:	Patient ID:
	Report Date:	Gender: M
		Requisition #:

TEST RESULTS

This individual is positive for the deleterious mutation KCNH2 Gly 657 Ser.

INTERPRETATION

KCNH2 Gly 657 Ser - Deleterious Mutation Found: This test result indicates the presence of the genetic mutation KCNH2 Gly 657 Ser. This mutation is a Class I variant, meaning it has either been functionally characterized as abnormal or is otherwise strongly expected to cause a familial arrhythmia-causing syndrome: Type 2 Long QT Syndrome (LQT2)(Hardman et al., J Biol Chem. 2007 Nov 2;282(44):31972-81. Epub 2007 Sep 6. (17823114)). Comprehensive clinical evaluation is strongly recommended to direct treatment decisions.

Based upon this test result, all first-degree relatives of this patient (offspring, siblings, parents) should undergo a careful clinical evaluation that includes a screening electrocardiogram and genetic testing to determine the presence or absence of this specific mutation. Evaluation, including genetic testing of extended relatives (second-degree relatives: grandparents /aunts /uncles /nieces /nephews; third-degree relatives such as cousins, great aunts/uncles, etc. and beyond), should be directed based upon the family history or guided by transmission pattern established following genetic test results of first-degree relatives. For example, if this mutation is detected in an affected individual's mother but not in the father, then all of the mother's first-degree relatives should receive thorough evaluation whereas the paternal side of the family would require no further evaluation.

To order the FAMILION Family Specific Test for family members of this patient, use the following Family Specific Code:

GPI-_____

This code must be included on the FAMILION Test Requisition/Payment Authorization Form (Form A) for the Family Specific Test.

Polymorphism(s) Found: This test result indicates identification of one or more genetic variants that have been identified previously in normal subjects and are considered polymorphisms (Class III variants). These variants are not likely arrhythmia syndrome-causing variants. Family screening for the presence of class III variants is not recommended.

RESULTS SUMMARY

Num	Gene	Region(G)	Nucl. Change	A.A. Change	Genotype	Region(P)	Region Type(P)	Class
1	KCNH2	exon 8	1969 G>A	Gly 657 Ser	G/A	S6	Transmembrane	I
2	KCNE1	exon 4	112 G>A	Gly 38 Ser	G/A	N-Terminal	N-Terminal	III
3	KCNH2	exon 11	2690 A>C	Lys 897 Thr	C/C	C-Terminal	C-Terminal	III

All Regions of Interest (100%) were successfully sequenced in the FAMILION Comprehensive Test for the genes KCNQ1 (LQT1), KCNH2 (LQT2), SCN5A (LQT3), KCNE1 (LQT5), KCNE2 (LQT6). Class IV variants, those genetic variants that are not expected to have any effect on the encoded protein, are not reported.

Limitations: This assay will not detect large DNA rearrangements or deletions and will not detect all errors in the RNA transcription or processing which are unrelated to coding sequence variants of DNA exons. Interpretation and classification of variants are subject to change in light of new evidence.

Methods: Genomic DNA was amplified by polymerase chain reaction to generate templates for direct sequencing of the complete open reading frame, splice junctions, and flanking regions of the genes KCNQ1, KCNH2, SCN5A, KCNE1, and KCNE2. See technical specifications for details.

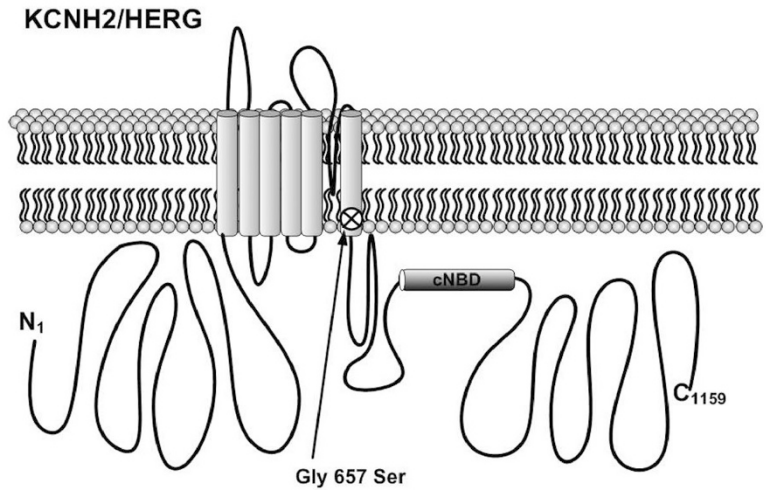
These test results should only be used in conjunction with the patient's clinical history and any previous analysis of the appropriate family members. It is strongly recommended that these test results be communicated to the patient in a setting that includes appropriate counseling. The results of this test are not intended to be used as the sole means for patient diagnosis or patient management decisions. The test was developed and its performance characteristics determined by Cogenics. The U.S. Food and Drug Administration (FDA) has not approved this test; however, FDA approval is not currently required for clinical use of this test. This test meets the requirements for high complexity tests under the Clinical Laboratory Improvement Amendments Act and its implementing regulations.

Authorized Signature:

Patricia D. Murphy, Ph.D., FACMG, Laboratory Director
Jessica K. Booker, Ph.D., FACMG, Associate Laboratory Director

X _____

This test is performed by Cogenics, Inc. , 5 Science Park, New Haven, CT 06511
CT License Number: CL-0633 CLIA Number: 07D0995237



APPENDIX 3

FAMILION®
GENETIC TESTS FOR INHERITED CARDIAC SYNDROMES

LQTS Test Report
(CONFIDENTIAL)

PHYSICIAN	SPECIMEN	PATIENT
Physician's Name:	Specimen Type: Blood	Patient's Name:
Hospital/Institution:	Draw Date:	Date of Birth:
	Receive Date:	Patient ID:
Mailing Address:	Report Date:	Gender: F
		Requisition #:

TEST RESULTS

This individual is positive for the possible deleterious mutation KCNQ1 Lys 362 Arg.

INTERPRETATION

KCNQ1 Lys 362 Arg - Possible Deleterious Mutation Found: This test result indicates the presence of the genetic mutation KCNQ1 Lys 362 Arg. This mutation is a Class II variant, meaning it is a type that may have the potential to cause a familial arrhythmia-causing syndrome: Type 1 Long QT Syndrome (LQT1) (Tester et al., Heart Rhythm. 2005 May;2(5):507-17 (15840476)). However, approximately 5% of reported healthy volunteers have been found to possess class II mutations. Therefore, extreme caution and comprehensive clinical evaluation are advised with respect to the incorporation of this variant information into treatment decisions.

Based upon this test result, all first-degree relatives of this patient (offspring, siblings, parents) should undergo a careful clinical evaluation that includes a screening electrocardiogram and genetic testing to determine the presence or absence of this specific mutation. Evaluation, including genetic testing of extended relatives (second-degree relatives: grandparents /aunts /uncles /nieces /nephews; third-degree relatives such as cousins, great aunts/uncles, etc. and beyond), should be directed based upon the family history or guided by transmission pattern established following genetic test results of first-degree relatives. For example, if this mutation is detected in an affected individual's mother but not in the father, then all of the mother's first-degree relatives should receive thorough evaluation whereas the paternal side of the family would require no further evaluation.

To order the FAMILION Family Specific Test for family members of this patient, use the following Family Specific Code:

GPI-_____

This code must be included on the FAMILION Test Requisition/Payment Authorization Form (Form A) for the Family Specific Test.

Polymorphism(s) Found: This test result indicates identification of one or more genetic variants that have been identified previously in normal subjects and are considered polymorphisms (Class III variants). These variants are not likely arrhythmia syndrome-causing variants. Family screening for the presence of class III variants is not recommended.

RESULTS SUMMARY

Num	Gene	Region(G)	Nucl. Change	A.A. Change	Genotype	Region(P)	Region Type(P)	Class
1	KCNQ1	exon 8	1085 A>G	Lys 362 Arg	A/G	C-Terminal	C-Terminal	II
2	KCNE1	exon 4	112 G>A	Gly 38 Ser	A/A	N-Terminal	N-Terminal	III

All Regions of Interest (100%) were successfully sequenced in the FAMILION Comprehensive Test for the genes KCNQ1 (LQT1), KCNH2 (LQT2), SCN5A (LQT3), KCNE1 (LQT5), KCNE2 (LQT6). Class IV variants, those genetic variants that are not expected to have any effect on the encoded protein, are not reported.

Limitations: This assay will not detect large DNA rearrangements or deletions and will not detect all errors in the RNA transcription or processing which are unrelated to coding sequence variants of DNA exons. Interpretation and classification of variants are subject to change in light of new evidence.

Methods: Genomic DNA was amplified by polymerase chain reaction to generate templates for direct sequencing of the complete open reading frame, splice junctions, and flanking regions of the genes KCNQ1, KCNH2, SCN5A, KCNE1, and KCNE2. See technical specifications for details.

These test results should only be used in conjunction with the patient's clinical history and any previous analysis of the appropriate family members. It is strongly recommended that these test results be communicated to the patient in a setting that includes appropriate counseling. The results of this test are not intended to be used as the sole means for patient diagnosis or patient management decisions. The test was developed and its performance characteristics determined by Cogenics. The U.S. Food and Drug Administration (FDA) has not approved this test; however, FDA approval is not currently required for clinical use of this test. This test meets the requirements for high complexity tests under the Clinical Laboratory Improvement Amendments Act and its implementing regulations.

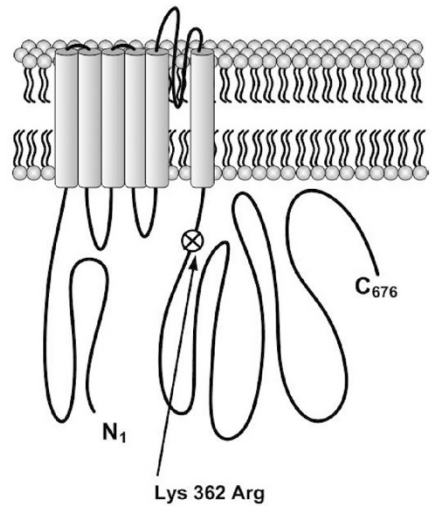
Authorized Signature:

Patricia D. Murphy, Ph.D., FACMG, Laboratory Director
Jessica K. Booker, Ph.D., FACMG, Associate Laboratory Director

X _____

This test is performed by Cogenics, Inc. , 5 Science Park, New Haven, CT 06511
CT License Number: CL-0633 CLIA Number: 07D0995237

KCNQ1/KVLQT1



APPENDIX 4

FAMILION®
GENETIC TESTS FOR INHERITED CARDIAC SYNDROMES

LQTS Test Report
(CONFIDENTIAL)

PHYSICIAN	SPECIMEN	PATIENT
Physician's Name: Hospital/Institution: Mailing Address:	Specimen Type: Blood Draw Date: Receive Date: Report Date:	Patient's Name: Date of Birth: Patient ID: Gender: M Requisition #:

TEST RESULTS

This individual is negative for deleterious mutations.

INTERPRETATION

No deleterious mutations (Class I or Class II variants) were found. This result is inconclusive and DOES NOT EXCLUDE the presence of a heritable disorder predisposing to cardiac arrhythmias, as variants in genomic regions not included in this test may play a causative role in such disorders. Among patients with a high clinical index of suspicion of disease, up to 25% of patients with LQTS and 70% of patients with Brugada Syndrome do not have deleterious mutations that would be identified with this test but may have deleterious mutations in other genes or in other regions of these genes.

Polymorphism(s) Found: This test result indicates identification of one or more genetic variants that have been identified previously in normal subjects and are considered polymorphisms (Class III variants). These variants are not likely arrhythmia syndrome-causing variants. Family screening for the presence of class III variants is not recommended.

RESULTS SUMMARY

Num	Gene	Region(G)	Nucl. Change	A.A. Change	Genotype	Region(P)	Region Type(P)	Class
1*	KCNH2	exon 13	3140 G>T	Arg 1047 Leu*	G/T	C-Terminal	C-Terminal	III

**The variant Arg 1047 Leu may be a susceptibility variant in dofetilide-induced Torsades de Pointes (Sun, et al., J Mol Cell Cardiol. 2004 Nov;37(5):1031-9).*

All Regions of Interest (100%) were successfully sequenced in the FAMILION Comprehensive Test for the genes KCNQ1 (LQT1), KCNH2 (LQT2), SCN5A (LQT3), KCNE1 (LQT5), KCNE2 (LQT6). Class IV variants, those genetic variants that are not expected to have any effect on the encoded protein, are not reported.

Limitations: This assay will not detect large DNA rearrangements or deletions and will not detect all errors in the RNA transcription or processing which are unrelated to coding sequence variants of DNA exons. Interpretation and classification of variants are subject to change in light of new evidence.

Methods: Genomic DNA was amplified by polymerase chain reaction to generate templates for direct sequencing of the complete open reading frame, splice junctions, and flanking regions of the genes KCNQ1, KCNH2, SCN5A, KCNE1, and KCNE2. See technical specifications for details.

These test results should only be used in conjunction with the patient's clinical history and any previous analysis of the appropriate family members. It is strongly recommended that these test results be communicated to the patient in a setting that includes appropriate counseling. The results of this test are not intended to be used as the sole means for patient diagnosis or patient management decisions. The test was developed and its performance characteristics determined by Cogenics. The U.S. Food and Drug Administration (FDA) has not approved this test; however, FDA approval is not currently required for clinical use of this test. This test meets the requirements for high complexity tests under the Clinical Laboratory Improvement Amendments Act and its implementing regulations.

Authorized Signature:

Patricia D. Murphy, Ph.D., FACMG, Laboratory Director
Jessica K. Booker, Ph.D., FACMG, Associate Laboratory Director

X _____

This test is performed by Cogenics, Inc. , 5 Science Park, New Haven, CT 06511
CT License Number: CL-0633 CLIA Number: 07D0995237

APPENDIX 5

5 Science Park
New Haven, CT 06511
P: 877.274.9432
F: 203.786.3418

March 3, 2008

Dr. XYZ
ADDRESS
CITY, STATE ZIP

Dear Dr. XYZ,

Thank you for referring your patient for the *FAMILION*® Test for cardiac ion channel mutations. Although the *FAMILION* Test did not identify any Class I or Class II mutations (see the *FAMILION* Technical Information Sheet for class definitions), this does not rule out a diagnosis of a cardiac channelopathy. In fact, based on current knowledge, approximately 25% of patients with a high index of suspicion for Long QT Syndrome (LQTS), 50% for Catecholaminergic Polymorphic Ventricular Tachycardia (CPVT) and 75% for Brugada Syndrome (BrS) will have a negative genetic test.

If your index of suspicion for an inherited heart rhythm disorder is high for this patient, research studies including mutational analysis for novel genetic mechanisms may be available. For information about current research genetic testing programs, please contact either of the following non-profit organizations that are dedicated to supporting and advocating for families with inherited heart rhythm disorders:

Cardiac Arrhythmias Research and Education Foundation (CARE)
(800) 404-9500
STOP SADS
www.longqt.org

Sudden Arrhythmia Death Syndromes (SADS) Foundation
(800) 786-7723 or (800)

www.sads.org

Respectfully,

Carol R. Reed, MD, FACP, FCCP
Executive Vice President and Chief Medical Officer for Clinical Data, Inc
cc: file

APPENDIX 6
Patents and applications for Long QT Syndrome (LQTS) genetic testing

Syndrome**	Gene	US Patent/application No.	Assignee/ Inventor
LQT1, JLN1	*KCNQ1*	US6150104[&], US6277978[&], US6342357, US6451534, US6582913, US6972176[#]	University of Utah Research Foundation
LQT2	*KCNH2*	**US5599673[#]**, **US6207383[#]**, US7297489[#]	University of Utah Research Foundation
LQT3	*SCN5A*	US6787309, **US5599673[#]**	University of Utah Research Foundation
		US2004126787A1	Inventors: Michael J Ackerman et al.
LQT5, JLN2	*KCNE1*	US6323026, **US6432644[#]**, US7247436[#]	University of Utah Research Foundation
LQT6	*KCNE2*	US6864364	University of Utah Research Foundation
LQT7	KCNJ2	US7306911	University of Utah Research Foundation
		US2005175995A1	Inventors: Louis Ptacek et al. (University of Utah)
LQT8	CACNA1C	US2008118438A1*	Inventors: Charles Antzelevitch et al.

Search query sample: "long QT" <in> Claims. Additional patents and applications identified by gene names (for e.g. *KCNJ2* or *Kir 2.1* for LQT 7) as search terms. All patents highlighted in gray are licensed to Bio-Reference Laboratories (BRLI, personal communication with Dr. Jorge Goldstein). Patents in bold were subject of 2002 patent infringement lawsuit brought by DNA Sciences against GeneDx (see Appendix 7).
**JLN1 and JLN2 = Jervell Lange-Nielsen syndrome variants; gene-syndrome correlations based on Saenen and Vrints, *J Mol Cell Cardiol,* 2008. 44(4): p. 633-46.
[&]Patent claims are on mutations associated *JLN1* only. [#]Indicates patents that declare use of federal funds and government interest. *Indicates claims including use of microarrays for diagnostic detection.

BRLI has obtained licenses to US6274332 and US6420124 from the University of Utah Research Foundation. The patents claim methods for screening drugs that can be used to treat individuals with mutations in *KCNE1* and *KCNQ1* respectively. BRLI also has licensed US7208273 from the University of Utah, which covers the detection of *SCN5A* polymorphisms for diagnosing drug-induced ventricular fibrillation.

Syndromes	Genes included	Patent/ Application No.	Inventors	Title
LQTS 1, 2, 3,5,6	*SCN5A*,*KCNQ1*, *KCNE1*, *KCNH2*,	US7179597	Raymond L Woosley (Georgetown Univ)	Genetic diagnosis for qt prolongation related adverse drug reactions
		US2005142591A1	Michael J Ackerman et al. (Mayo clinic)	Method of genetic testing in heritable arrhythmia syndrome patient
LQT1,2,3,5,6	*SCN5A*, *KCNQ1*, *KCNE1*, *KCNH2*, *KCNE2*	US7179597*	Raymond L Woosley (Georgetown Univ)	Genetic diagnosis for QT prolongation related adverse drug reactions
LQT2, LQT3, LQT1/JLN1	*KCNH2*, *SCN5A*,*KCNQ1*	US2005130190A1*	Charles Antzelevitch, Ramon Brugada et al. (Masonic Medical Research Lab)	Mutations in ion channel proteins associated with sudden cardiac death
LQT8 SCD	CACNA1C, CACNB2	US2008118438A1*	Charles Antzelevitch & Guido Pollevick. (Masonic Medical Research Lab)	Loss of function mutations in calcium channel polypeptides associated with sudden cardiac death
LQT3, LQT1/JLN1 LQT8	*SCN5A*,*KCNQ1*, CACNA1C	US2005287574A1	Medtronic Inc	Genetic diagnostic method for SCD risk stratification

SCD – Sudden Cardiac Death *Indicates applications and patents including claims on the use of microarrays for diagnostic detection.

APPENDIX 7

Eric R. Lamison (State Bar No. 178262)
KIRKLAND & ELLIS
777 S. Figueroa Street
Los Angeles, California 90017
Telephone: (213) 680-8400
Facsimile: (213) 680-8500

Mark A. Pals
Lauren Hennessey Breit
KIRKLAND & ELLIS
200 East Randolph Drive
Chicago, Illinois 60601
Telephone: (312) 861-2000
Facsimile: (312) 861-2200

Attorneys for Plaintiff
DNA SCIENCES, INC.

COPY

FILED
NOV 22 2002
RICHARD W. WIEKING
CLERK, U.S. DISTRICT COURT
NORTHERN DISTRICT OF CALIFORNIA

E-filing

UNITED STATES DISTRICT COURT

NORTHERN DISTRICT OF CALIFORNIA

SAN FRANCISCO DIVISION

DNA SCIENCES, INC., Plaintiff, vs. GENEDX, INC., Defendant.	C 02 5578 CRB Civil Action No. **COMPLAINT FOR PATENT INFRINGEMENT; DEMAND FOR JURY TRIAL; CERTIFICATION OF INTERESTED PARTIES OR PERSONS**

Plaintiff, DNA Sciences, Inc., by its undersigned attorneys, for its Complaint against GeneDX, Inc., demands a jury trial and alleges as follows:

NATURE OF THE ACTION

1. This is an action for patent infringement arising under the patent laws of the United States, 35 U.S.C. §§ 1 *et seq.*

THE PARTIES

2. Plaintiff, DNA Sciences, Inc. ("DNA Sciences") is incorporated under the laws of the State of Delaware, having its principal place of business at 6540 Kaiser Drive, Fremont, California 94555.

3. On information and belief, Defendant GeneDX, Inc. ("GeneDX") is incorporated under the laws of the State of Maryland and has its principal place of business at 207 Perry Parkway, Gaithersburg, Maryland 20877.

JURISDICTION AND VENUE

4. This Court has subject matter jurisdiction over this action pursuant to 28 U.S.C. §§ 1331 and 1338(a).

5. This Court has personal jurisdiction over Defendant GeneDX as it has substantial contacts with the state of California and has committed acts of infringement within this district.

6. Venue properly lies in this District pursuant to 28 U.S.C. §§ 1391 and 1400(b).

INTRADISTRICT TRANSFER

7. This case is an Intellectual Property Action under Local Rule 3-2(c), excepted from the categories providing for assignment by the Clerk to particular county Courthouses.

FACTS COMMON TO ALL COUNTS

8. DNA Sciences is an applied genetics company focused on the discovery and commercialization of tests for diagnosis and treatment of disease based upon variations in DNA sequence.

9. On information and belief, GeneDX provides DNA diagnostic services, including genetic testing for the purpose of diagnosis, carrier detection, and prenatal testing.

10. On information and belief, GeneDX has offered and continues to offer genetic testing for Long QT Syndrome, also known as Romano Ward syndrome (dominant) and Jervell, Lange-Nielsen syndrome (autosomal recessive), *inter alia* via its interactive website at www.genedx.com.

11. DNA Sciences is the exclusive licensee of, and has the right to enforce, U.S. Patent No. 6,432,644 ("the '644 Patent"), entitled "MUTATIONS IN THE KCNE1 GENE ENCODING HUMAN MINK WHICH CAUSE ARRHYTHMIA SUSCEPTIBILITY THEREBY ESTABLISHING KCNE1 AS AN LQT GENE," duly and legally issued on August 13, 2002 (attached hereto as exhibit A).

12. DNA Sciences is the exclusive licensee of, and has the right to enforce, U.S. Patent No. 6,207,383 ("the '383 Patent"), entitled "MUTATIONS IN AND GENOMIC STRUCTURE OF

HERG—A LONG QT SYNDROME GENE," duly and legally issued on March 27, 2001 (attached hereto as exhibit B).

13. DNA Sciences is the exclusive licensee of, and has the right to enforce, U.S. Patent No. 5,599,673 ("the '673 Patent"), entitled "LONG QT SYNDROME GENES," duly and legally issued on February 4, 1997 (attached hereto as exhibit C).

14. On information and belief, GeneDX has actual notice of the existence of the above mentioned patents.

COUNT I - INFRINGEMENT OF THE '644 PATENT

15. DNA Sciences repeats and realleges the allegations of paragraphs 1 through 14 as though fully set forth herein.

16. On information and belief, GeneDX has infringed, and is still infringing, either literally or under the doctrine of equivalents, one or more claims of the '644 Patent by making, using, importing, offering for sale, and/or selling genetic testing for Long QT syndrome using methods covered by the '644 patent.

17. On information and belief, GeneDX's infringement has injured or will injure DNA Sciences and DNA Sciences is or will be entitled to recover damages adequate to compensate it for GeneDX's infringement.

18. On information and belief, GeneDX's infringement has been deliberate, willful, intentional, and with full knowledge of the existence of the '644 patent.

19. GeneDX has caused DNA Sciences substantial damage and irreparable injury by its continuing infringement of the '644 Patent and DNA Sciences will continue to suffer damage and irreparable injury unless and until GeneDX is enjoined by this Court from continuing such infringement.

20. DNA Sciences is entitled to injunctive and compensatory relief, including attorneys' fees, under 35 U.S.C. §§ 271, 281, and 283-285.

COUNT II - INFRINGEMENT OF THE '383 PATENT

21. DNA Sciences repeats and realleges the allegations of paragraphs 1 through 14 as though fully set forth herein.

22. On information and belief, GeneDX has infringed, and is still infringing, either literally or under the doctrine of equivalents, one or more claims of the '383 Patent by making, using, importing, offering for sale, and/or selling genetic testing for Long QT syndrome using methods covered by the '383 patent.

23. On information and belief, GeneDX's infringement has injured or will injure DNA Sciences and DNA Sciences is or will be entitled to recover damages adequate to compensate it for GeneDX's infringement.

24. On information and belief, GeneDX's infringement has been deliberate, willful, intentional, and with full knowledge of the existence of the '383 patent.

25. GeneDX has caused DNA Sciences substantial damage and irreparable injury by its continuing infringement of the '383 Patent and DNA Sciences will continue to suffer damage and irreparable injury unless and until GeneDX is enjoined by this Court from continuing such infringement.

26. DNA Sciences is entitled to injunctive and compensatory relief, including attorneys' fees, under 35 U.S.C. §§ 271, 281, and 283-285.

COUNT III - INFRINGEMENT OF THE '673 PATENT

27. DNA Sciences repeats and realleges the allegations of paragraphs 1 through 14 as though fully set forth herein.

28. On information and belief, GeneDX has infringed, and is still infringing, either literally or under the doctrine of equivalents, one or more claims of the '673 Patent by making, using, importing, offering for sale, and/or selling genetic testing for Long QT syndrome using methods covered by the '673 patent.

29. On information and belief, GeneDX's infringement has injured or will injure DNA Sciences and DNA Sciences is or will be entitled to recover damages adequate to compensate it for GeneDX's infringement.

30. On information and belief, GeneDX's infringement has been deliberate, willful, intentional, and with full knowledge of the existence of the '673 patent.

31. GeneDX has caused DNA Sciences substantial damage and irreparable injury by its continuing infringement of the '673 Patent and DNA Sciences will continue to suffer damage and irreparable injury unless and until GeneDX is enjoined by this Court from continuing such infringement.

32. DNA Sciences is entitled to injunctive and compensatory relief, including attorneys' fees, under 35 U.S.C. §§ 271, 281, and 283-285

PRAYER FOR RELIEF

WHEREFORE, DNA Sciences respectfully requests that Judgment be entered in favor of DNA Sciences and against GeneDX and that DNA Sciences be granted the following relief:

(i.) A declaration that GeneDX has infringed and is infringing the '644, '383, and '673 Patents;

(ii.) A declaration that the aforementioned infringement of the '644, '383, and '673 Patents has been and is willful;

(iii.) Entry of a permanent injunction restraining GeneDX, its officers, agents, employees, attorneys, and all others in active concert or participation with GeneDX from further acts of infringement of the '644, '383, and '673 Patents, pursuant to 35 U.S.C. § 283;

(iv.) An award of damages sufficient to compensate DNA Sciences for GeneDX's infringement of the '644, '383, and '673 Patents, pursuant to 35 U.S.C. § 284;

(v.) An award of prejudgment and post judgment interest, pursuant to 35 U.S.C. § 284;

(vi.) An award of increased damages in an amount not less than three times the amount of damages found by the jury or assessed by this court for GeneDX's willful infringement, pursuant to 35 U.S.C. § 284;

(vii.) A declaration that this case is "exceptional" under 35 U.S.C. § 285 and awarding DNA Sciences its reasonable attorney's fees, expenses, and costs incurred in this action, pursuant to 35 U.S.C. § 284; and

(viii.) Such other and further relief as this Court shall deem appropriate.

DATED: November 21, 2002

KIRKLAND & ELLIS

By: _____

Eric R. Lamison
KIRKLAND & ELLIS
777 S. Figueroa Street
Los Angeles, CA 90017
Telephone: (213) 680-8400
Facsimile: (213) 680-8500

Mark A. Pals
Lauren Hennessey Breit
KIRKLAND & ELLIS
200 East Randolph Drive
Chicago, IL 60601
Telephone: (312) 861-2000
Facsimile: (312) 861-2200

Attorneys For Plaintiff
DNA SCIENCES, INC

DEMAND FOR TRIAL BY JURY

Plaintiff DNA Sciences, Inc. hereby demands a jury trial of all issues triable to a jury in this action

DATED: November 21, 2002

KIRKLAND & ELLIS

By: _____

Eric R. Lamison
KIRKLAND & ELLIS
777 S. Figueroa Street
Los Angeles, CA 90017
Telephone: (213) 680-8400
Facsimile: (213) 680-8500

Mark A. Pals
Lauren Hennessey Breit
KIRKLAND & ELLIS
200 East Randolph Drive
Chicago, IL 60601
Telephone: (312) 861-2000
Facsimile: (312) 861-2200

Attorneys For Plaintiff
DNA SCIENCES, INC

CERTIFICATION OF INTERESTED ENTITIES OR PERSONS

Pursuant to Civil L.R. 3-16, the undersigned certifies that the following listed persons, associations of persons, firms, partnerships, corporations (including parent corporations) or other entities (i) have a financial interest in the subject matter in controversy or in a party to the proceeding, or (ii) have a non-financial interest in that subject matter or in a party that could be substantially affected by the outcome of this proceeding:

1. University of Utah Research Foundation

This entity has a financial and non-financial interest in the subject matter in controversy as the assignee of record for the patents being asserted and licensor of the underlying patent rights to DNA Sciences, Inc.

2. Yale University

This entity has a non-financial interest in the subject matter in controversy as the licensor of related patent rights to DNA Sciences, Inc.

3. WebMD Corporation

This entity has a financial interest in DNA Sciences, Inc. as a shareholder.

4. Pharmaceutical Product Development, Inc. (PPD, Inc.)

This entity has a financial interest in DNA Sciences, Inc. as a shareholder.

DATED: November 21, 2002

KIRKLAND & ELLIS

By: _____

Eric R. Lamison
KIRKLAND & ELLIS
777 S. Figueroa Street
Los Angeles, CA 90017
Telephone: (213) 680-8400
Facsimile: (213) 680-8500

Mark A. Pals
Lauren Hennessey Breit
KIRKLAND & ELLIS
200 East Randolph Drive
Chicago, IL 60601
Telephone: (312) 861-2000
Facsimile: (312) 861-2200

Attorneys For Plaintiff
DNA SCIENCES, INC

AGREEMENT

This Agreement is made on this ___ day of December, 2002 (the "Effective Date") by and between DNA Sciences, Inc., a Delaware corporation having its principal place of business at 6540 Kaiser Drive, Fremont, California 94555 ("DNA Sciences"), and GeneDX, Inc., a Maryland corporation having its principal place of business at 207 Perry Parkway, Gaithersburg, Maryland 20877 ("GeneDX").

RECITALS

WHEREAS, DNA Sciences initiated litigation against GeneDX under U.S. Patent Nos. 6,432,644, 6,207,383, and 5,599,673 ("the Patents") in the Northern District of California, Case No. C 02-5578 CRB (the "Patent Litigation"), and the parties now wish to resolve their differences at issue in the Patent Litigation.

NOW THEREFORE, in consideration of the foregoing and the mutual covenants and obligations herein undertaken, the parties agree as follows:

1. Within ten (10) days of the Effective Date, DNA Sciences shall voluntarily dismiss the Patent Litigation, without prejudice.

2. GeneDX admits that its manufacture, use, offer to sell, or sale of tests or services relating to the diagnosis of Long QT syndrome, Romano Ward syndrome (dominant), and Jervell, Lange-Nielsen syndrome (autosomal recessive), infringes at least one claim of at least one of the Patents.

3. GeneDX shall immediately cease to make, use, offer for sale and sell: (i) tests or services relating to the diagnosis of Long QT syndrome, Romano Ward syndrome (dominant), and Jervell, Lange-Nielsen syndrome (autosomal recessive) and (ii) any other test or any services relating to diagnosis of Long QT syndrome using methods that would be covered by a claim of any of the Patents.

4. With respect to any samples that arrive or arrived at GeneDX for any such testing or service after November 25, 2002, GeneDX, to the extent it has not already done so prior to the Effective Date, shall refuse all such samples and/or shall refuse to perform such testing or service.

5. Within two (2) days of the Effective Date, GeneDX shall remove or cause to be removed all mention of its tests or services for detecting mutations associated with Long QT syndrome, Romano Ward syndrome, and Jervell, Lange-Nielsen syndrome from its website, GeneTest's website, and any other website to which GeneDX provides content or offers its services.

6. GeneDX admits that the Patents are valid and enforceable, and agrees that it will not, directly or indirectly, aid, assist or participate in any action contesting the validity or enforceability of any Patent or any claims thereof.

7. Nothing herein shall be interpreted as DNA Sciences, directly or indirectly, granting GeneDX any right or license, express or implied, to any of the Patents.

8. DNA Sciences hereby releases and discharges GeneDX from any damages arising from GeneDX's infringement of the Patents occurring prior to the Effective Date, but only so long as GeneDX abides by the terms of this Agreement.

9. Each party consents to the jurisdiction of the United States federal courts for the Northern District of California and, if applicable, the state courts located in San Francisco County, California, U.S.A. for any legal action, suit, or proceeding arising under or relating to this Agreement or any future infringement claim by DNA Sciences under any of the Patents, and agrees that any such action, suit, or proceeding may be brought only in such courts. Each party further waives any objection to the laying of venue for any such suit, action, or proceeding in such courts.

10. The terms of this Agreement shall be binding upon GeneDX and its respective directors, officers, agents, employees, representatives, controlled affiliates, subsidiaries, successors and assigns.

11. This Agreement constitutes the entire agreement between DNA Sciences and GeneDX with respect to the subject matter discussed herein, and supersedes all prior agreements, negotiations and understandings relating to such subject matter. This Agreement shall not be modified, altered, or amended unless in writing signed by both parties. This Agreement shall be governed by the laws of the state of California.

IN WITNESS WHEREOF, the parties hereto, by and through their duly authorized undersigned representatives, have executed this Agreement on the dates indicated below.

DNA SCIENCES, INC.	**GENEDX, INC.**
By: _____	By: _____
Name: _____	Name: _____
Title: _____	Title: _____
Date: December ____, 2002	Date: December ____, 2002

APPENDIX 8

GeneDx, Inc.
207 Perry Parkway
Gaithersburg, MD 20877
Phone (301) 519-2100
Fax (301) 519-2892
E-mail: genedx@genedx.com
www.genedx.com

Information Sheet

Genetic testing for Long QT Syndrome (LQTS)

Also known as: Romano Ward syndrome (RWS), dominant; Jervell, Lange-Nielsen syndrome (JLNS), autosomal recessive

Mendelian Inheritance in Man Number: RWS, 192500; JLNS, 220400

Clinical features:

Cardiovascular disorder characterized by an abnormality in cardiac repolarization leading to a prolonged QT interval on the surface ECG. LQTS causes syncope and sudden death usually in young, otherwise healthy individuals. Romano-Ward syndrome is the most common form. Jervell, Lange-Nielsen syndrome is associated with congenital sensorineural deafness.

Inheritance pattern:

Two inherited forms of LQTS exist. Romano-Ward syndrome is inherited in a dominant manner and has variable penetrance. The offspring of an affected individual has a 50% risk of also being affected. Jervell, Lange-Nielsen syndrome is inherited in an autosomal recessive manner, with both parents carrying a mutation. The risk of inheritance of the Jervell, Lange-Nielsen syndrome to the offspring of such parents is 25%. However, the risk of inheriting just one abnormal gene from one parent, and having autosomal dominant (Romano-Ward) syndrome without deafness is 50%.

Indications for direct DNA testing:

1. Confirmation of clinical diagnosis
2. Genetic counseling for affected individuals
3. Pre-symptomatic testing of family members
4. Development of a medical surveillance plan and prophylaxis for mutation carriers
5. Prenatal diagnosis

Test methods:

Using genomic DNA obtained from buccal (cheek) swabs, the most frequently mutated exons of the five genes associated with this disorder are screened as follows: 8 exons of KCNQ1, (also known as KVLQT1) (exons 3, 5, 6, 7, 8, 12, 13, 15), five exons of HERG (exons 2, 6, 7, 9, 10), two exons of SCN5A (exons 26 and 28), the single coding exons of KCNE1 and KCNE2. In families where several affected individuals are available for study, linkage analysis is available to identify or rule-out the

involvement of specific genes prior to sequence analysis. JLN clinical features would dictate a primary screen in KCNQ1 (all 10 exons) and the single coding exon of KCNE1.

Test sensitivity:

Published data shows that 42% of the total mutations identified in the disorder occur in KCNQ1 (KVLQT1), 45% in HERG, 8% in SCN5A, 3% in KCNE1, and 2% in KCNE2. Using our screening approach described above, **we would detect 87% of the LQTS mutation that occur in these genes**. However, only about 68% of patients with LQTS have been found to have a mutation in one of these five genes, suggesting that there are other genes yet to be identified. We thus calculate **the overall sensitivity of our test methods to detect an LQTS-associated mutation to be 59%.**

Mutational spectrum:

Most LQTS mutations occur in KCNQ1 and HERG, accounting equally for a total of almost 90% of identifiable mutations. A large majority of the mutations are missense mutations that disrupt the activity of the potassium or sodium channel ventricular repolarization of the heart.

Costs and turn-around time:

Mutation detection in a new patient is $2200 for all five LQTS genes to be screened. Charges are assessed only for the LQTS genes actually screened. For testing a new patient, turn-around time is approximately 6-8 weeks, but will be longer if the entire set of 5 genes must be screened.

KCNQ1 and KCNE1 are preferentially screened if the patient has a Jervell, Lange-Nielsen clinical diagnosis, for a fee of $1300.

Pre-natal diagnosis using two samples (CVS, fresh amniocytes and/or cultured amniocytes) is $700. There may be an additional cost for ruling out maternal contamination of the fetal sample, in some cases. For pre-natal diagnoses, where the mutation in the family is known, turn-around time is approximately 2 weeks. Fees are subject to change without notice.

CPT codes for LQTS-associated gene mutation tests in Long QT Syndrome (full gene screen)

83891 x 20 units = $ 180
83898 x 20 units = $ 500
83894 x 20 units = $ 200
83904 x 40 units = $1200
83892 x 4 units = $ 40
83912 x 4 units = $ 80

TOTAL = $2200

Possible ICD9 Codes

Cardiac dysrhythmia, NOS	427.9
Ventricular fibrillation	427.41
Syncope and collapse	780.2