SPOTLIGHT ON GENETICS

Changing the sequence of events

Young researchers need to get with the program for the chance to make the most of a new generation of DNA technology

"I don't get to meet the patients, but I always keep them in mind as I look at the data. Getting it right is so important for them."

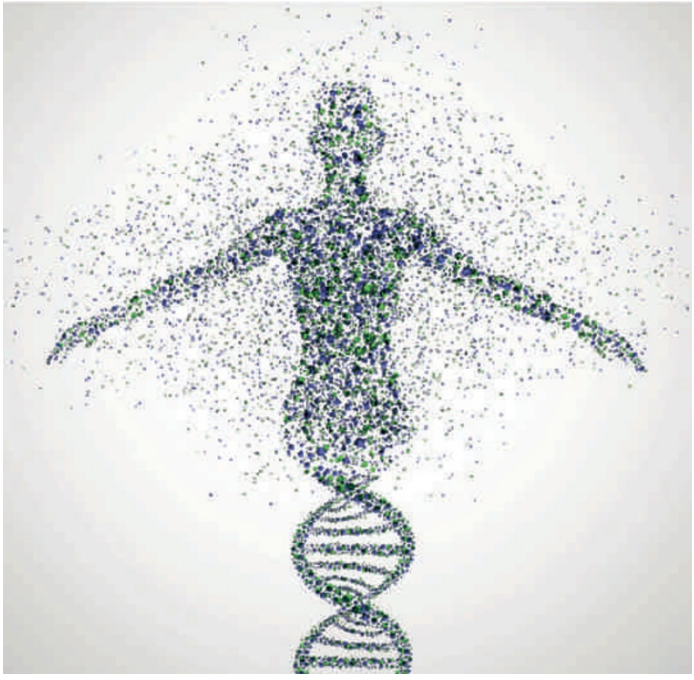
Jillian Casey, National Children's Research Centre at Our Lady's Children's Hospital, Crumlin.

AS A young graduate student, Elliott Margulies led a double life. By day he dissected mice in the lab. By night he read books that promised to teach him 'how to program in 21 days'.

Having trained in genome science during his PhD, Margulies was working at the National Human Genome Research Institute (NHGRI), in Maryland, Bethesda. He had entered the field of genome science as a revolution was underway and rightly predicted that programming skills would be useful.

Since the publication of the human genome sequence in 2001, there have been seismic increases in the speed and decreases in the cost of genetic sequencing. This is largely down to what are known as second- or next-generation sequencing technologies that allow parallel sequencing of numerous DNA strands simultaneously. In 2001 it cost more than US$95 million to sequence a human-size genome, today it costs less than $6,000. These improvements also mean that entire genomes and sections that might be implicated in disease can be sequenced faster than ever before. "In the past four years the process of sequencing has changed tremendously," says Richard Smith, director of the Iowa Institute of Human Genetics at the University of Iowa. "Now you can do substantially more, tremendously faster."

This technology has brought new opportunities, including the chance to study rare diseases and variants that were out of reach for geneticists in the past. But the pace and scale of possibility for genetic sequencing also calls for a different set of skills, as Margulies can testify. Those night shifts paid off and today he is director of scientific research at Illumina, one of the leading global companies in genetic sequencing and analysis. "Computing skills these days are a must" for geneticists wanting to make waves in genome science, he says. And they are just one in a range of tools needed by those wanting to exploit the capability of new sequencing technologies.



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BAYLOR COLLEGE OF MEDICINE

Baylor College of Medicine.

Number crunchers

Genetics has always been a quantitative area of biology, but with advances in sequencing, which involve crunching vast quantities of data, a background in mathematics is becoming increasingly valuable.

With more than 30 publications to his name, Manuel Rivas, a final year PhD student at the University of Oxford, has already made important contributions to human genetics. But the last time he did any wet biology was at high school. It was during his undergraduate degree in mathematics at MIT that Rivas realised he could apply his mathematical acumen to human genetics, and became hooked. Since then he has gone on to study the contribution of rare genetic variants to complex diseases. "An interest in mathematics and computing is going to be immeasurably advantageous," agrees Richard Houlston, professor of molecular and population genetics at the Institute of Cancer Research in London, UK.

The importance of mathematicians in genetics—particularly those with strength in statistics—became clear by the mid 2000s when human geneticists were scanning large swathes of people to search for the genetic basis of common diseases such as diabetes, obesity or schizophrenia; what became known as genome wide association studies (GWAS).

GWAS can identify common variants, each of which makes a small contribution to the studied trait. For many studies, groups that can number hundreds of thousands of subjects are required, along with sophisticated analyses of the data. Not all researchers working with complex traits can analyse the vast amounts of

Cost of DNA sequencing

Date	Cost per megabase of DNA sequence	Cost per human-sized genome
Sep-01	$5,292.39	$95,263,072
Sep-02	$3,413.80	$61,448,422
Oct-03	$2,230.98	$40,157,554
Oct-04	$1,028.85	$18,519,312
Oct-05	$766.73	$13,801,124
Oct-06	$581.92	$10,474,556
Oct-07	$397.09	$7,147,571
Oct-08	$3.81	$342,502
Oct-09	$0.78	$70,333
Oct-10	$0.32	$29,092
Oct-11	$0.09	$7,743
Oct-12	$0.07	$6,618
Apr-13	$0.06	$5,826

Source: National Human Genome Research Institute

First hand: Jillian Casey


PETER CASEY

Jillian Casey had a pretty good start to her PhD. Her first task at University College Dublin in 2008 was to analyse DNA from a family where many members had a rare condition that affected eye development. "The family had been waiting for nine years for a genetic diagnosis," she says.

Previous work had excluded all the genes known to cause this disorder and suggested that the family had a new genetic variant, but the gene and its mutation remained a mystery. But using the latest SNP arrays —which can be used to search for differences between whole genomes—Casey was able to quickly compare DNA from healthy and affected family members.

Within a week she had narrowed the search to a segment containing a handful of genes. "Eight weeks later, using next generation sequencing, we had the actual mutation," she recalls. "And with that I saw how these new technologies could make it much faster to find these rare disease genes."

Since then, Casey has helped to isolate specific mutations in several other rare diseases, particularly diseases that affect children.

"For some families a correct genetic diagnosis can mean closure, and it can help them understand the risk for future children," says Casey. "Sometimes knowing the mutation can mean clinicians can manage the rare disease more effectively."

Casey, who studied genetics as an undergraduate at University College Cork, recommends that students take modules on statistics and bioinformatics where possible. Internships in genetics labs or companies can also be a good way to get started and build wet lab skills at the bench, she says.

Since 2011 she has been working as a post-doc with the National Children's Research Centre at Our Lady's Children's Hospital, Crumlin, where she continues to look for the genes responsible for rare disorders in families. "I don't get to meet the patients, I get an anonymised tube of DNA," she says. "But I always keep the patient and the family in my mind as I look at the data. Getting it right is so important for them."

GWAS data, but an in-depth appreciation of the statistical challenges involved is necessary.

Suzanne Leal, professor of molecular and human genetics at Baylor College of Medicine advises biologists to take statistics courses early in their career. Having a grounding in statistics could help further a career more quickly, she says. Usually five years of postdoc in a wet lab is required before applying for independent positions, whereas those with expertise in statistic are more likely to make that move after just two.

Rare finds

The large quantities of data generated by GWAS are dwarfed by the masses of genetic information that can be sequenced with next-generation technologies. Both exome sequencing – which targets the areas of the genome involved in protein coding – and whole genome sequencing, can now be used to look for the causes of much rarer diseases [see 'First hand: Jillian Casey']. This is great news for patients, says Rolf Sijmons, professor of medical translational genetics at the University of Groningen in the Netherlands. "We are now putting together a program in the Groningen University Medical Center to sequence the exome of newborn babies within a few days. This would have been pure science fiction a few years ago."

The ability to analyse this type of data—known as bioinformatics—is therefore increasingly important, says Smith, whose research into rare renal disease and hearing loss uses next generation sequencing. He says since he started in the field in the early eighties, he's seen the skill requirement shift from mainly wet lab work to a larger focus on bioinformatics: "those components are now essentially equal."

Happily, there's no need to stay up teaching yourself new skills as Margulies did. Bioinformatics courses, including short courses that can bring you up to speed on how to handle the data, are offered in most institutions. "As you begin your career path I think it's important to understand the many ways to manipulate the data," says Smith. Even if you cannot perform all the analyses yourself, a thorough understanding will enable you to converse with the experts.

In the field there is also an increasing emphasis on collaboration, so good communication skills and a desire to be part of a team are essential. Understanding and interpreting genetic data will require unprecedented collaboration between scientists with different backgrounds, says Sijmons: "genomics and its translation into healthcare is very much a multidisciplinary science. Having to work with different types of professionals is one of the most interesting and stimulating aspects of my job." At Illumina, Margulies routinely works closely with chemists, physicists, computer programmers and material scientists. The social skills required are one of the key attributes Sijmons looks for when recruiting new PhD students to his lab.

Taking genomics to the clinic

The benefits of sequencing are not confined to the lab. Han Brunner, professor of medical genetics at the Radboud University Nijmegen Medical Centre, in the Netherlands, says that the role of dismorphologists—specialists who diagnose a patient with a rare disease based on a set of physical characteristics—is disappearing. The Nijmegen next year plans to introduce exome sequencing as the basis for all genetic diagnoses at the centre. Getting clinical geneticists ready for this transition is a major challenge, but Brunner sees it as an invaluable move for patients.

Eventually this changed skill-base will be represented in the early education of medical students, says Smith. "The healthcare provider will need to understand large datasets and the limitations of the data they are looking at. So there's going to be a change in the education of the medical student."

Perhaps the biggest breakthrough that remains for sequencing technology is working out the exact role newly-identified genetic variants play in disease biology. Sijmons says the technology will lead to new insights that will offer significant new opportunities to prevent and treat diseases. And with those improvements, the rewards for those working in the field are "potentially gigantic," he says. Indeed, agrees Smith, the changes he's seen in the last few years are so exciting, he wishes he could stay in the field for longer. "I feel like I have the best job in the world. The only problem is now I'm 60. I wish I was 40 and had that much longer to go." ■

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LSUHealth NewOrleans

Professor and Department Head Department of Genetics

Louisiana State University Health Sciences Center School of Medicine, New Orleans

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The successful candidate will demonstrate a commitment to biomedical research and education and will have documented leadership ability and the capacity to provide a vision of excellence for the Department. Achievements in multi-disciplinary, collaborative research, mentorship, teaching, and administration are essential; candidates must be committed to promoting an inclusive environment in the Department. The incumbent will be responsible for all facets of activity in the department, including both graduate and undergraduate medical education, faculty recruitment and retention, and development of research programs. He/she will be expected to coordinate the development of departmental and collaborative research programs within the school and with our academic partners. We are especially interested in candidates who can forge strong collaborative research programs, such as program/project and center grants and funded training programs, and candidates who will foster meaningful translational research programs.

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