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Cesarean delivery doesn't stop bone fractures in newborns with OI

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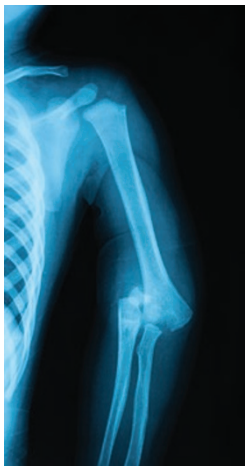

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The combination of ultrasound and genetic technologies has led to increased prenatal diagnosis of rare genetic disorders, resulting in changes to health-care planning for mother and fetus. One such change revolves around prenatal diagnosis of osteogenesis imperfecta (OI), a cluster of genetic disorders that increase the risk of bone fragility and fractures. Cesarean delivery (CD) has been suggested as a less traumatic form of delivery for OI cases, but there has been no clinical evidence to support this supposition. Here, Bellur et al. provide the first statistically significant evidence that there is no difference in risk of fracture between CD and vaginal birth.

Using data from 540 individuals enrolled in a longitudinal study of OI at five institutions, investigators analyzed several factors, including mode of delivery, on the at-birth fracture rates. The single most important predictor of fracture was the subtype of OI, with the more severe forms being highly likely to sustain fracture, regardless of birth method. The researchers point out that the conclusions are limited by the fact that all data were self-reported and could not be confirmed by a review of medical records. However, they conclude that CD should not be performed for the sole purpose of preventing fracture. Currently, the Brittle Bone Disease Consortium, a rare disease clinical research network supported by the National Institutes of Health, is conducting a follow-on study to extend its utility and to help in developing guidelines for the management of pregnancy in OI. —*Karyn Hede, News Editor*

False positives: an ever-present risk in genomic screening

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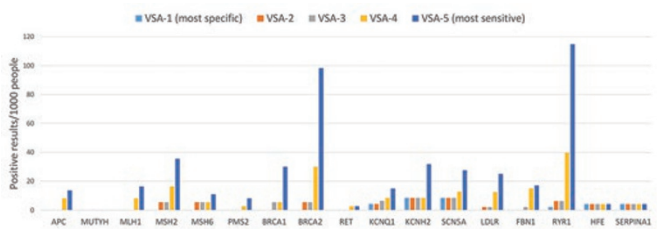

With widespread genomic screening gaining ground, the issue of false-positive results remains the elephant in the room. Large-scale genomic sequencing initiatives of healthy adults are under way in many places, but no standards have been put in place to ensure maximum benefit to participants while minimizing the risk of harm. Indeed, for most conditions, the true clinical sensitivity and specificity of genetic testing have not been established. To better understand how to best present genomic results to testing participants, the Center for Genomics and Society at the University of North Carolina at Chapel Hill is exploring the best way to set criteria for return of positive test results. The GeneScreen study's initial findings, presented in this issue, show that even small tweaks to specificity greatly increase false positives for the 17 clinically actionable genes studied.

Starting with the premise that false positives for clinically significant genetic alterations have a high probability of resulting in unnecessary interventions, the research team explored ethical considerations of screening 1,000 adults from the general population. Using massively parallel sequencing of 17 genes responsible for 11 conditions, they developed five algorithms with differing sensitivity cutoffs for flagging a positive result. They found that, for instance, decreasing specificity for calling variants in the *BRCA1* gene to even 99% resulted in a positive predictive value of only 37% among the general population. The investigators also point out that even when pathogenic variants are correctly identified, the associated disease may never manifest itself due to reduced penetrance, increasing the risk of overdiagnosis even when variants are called correctly. Given the current limited ability to interpret the true pathogenic potential of carrying rare genomic variations, the researchers emphasize that a very high threshold should be used for calling pathogenic variants and care must be taken to understand the potential negative consequences of screening in the general population. —*Karyn Hede, News Editor*

Check those checklists: a handy guide to reporting guidelines

Many reporting guidelines have been formulated over the years in an effort to ensure the quality of published articles. However, the number of reporting guidelines can be overwhelming. Just look at two places that list guidelines: the National Library of Medicine's Research Reporting Guidelines and Initiatives (http://1.usa.gov/1WsKiwN) and EQUATOR (http://bit.ly/1TRWp2r). By our count, there are more than 300 guidelines, with a bewildering (and highly entertaining) array of acronyms ranging from the zoological RATS (http://bit.ly/1WteYxh) and MOOSE (http://bit.ly/1Tdm5q3) to the rather startling STARE (http://1.usa.gov/1T9cjmw), to the frankly inexplicable INANE (http://bit.ly/1rIokIV).

But let's not lose sight of the forest for the trees. These guidelines exist to promote high-quality published research and to allow us to compare different studies and outcomes.

RESEARCH HIGHLIGHTS

Guidelines are important for the cornerstone of research: reproducibility. While other checklists are optional (but encouraged), at the request of the National Institutes of Health, *GIM* introduced its first mandatory checklist on transparency of reporting and the reproducibility of published results last year, focusing on elements of methodological information that are usually poorly reported. Authors are asked for that list at the revision stage. To help prospective authors navigate publishing guidelines, *GIM* has culled other guidelines that apply to the types of studies we publish, and we present them here.

Our goal is not to burden our authors (not to mention reviewers and editors) with busywork. *GIM* has always followed rigorous publication guidelines—those of the Committee on Publication Ethics (COPE; http://bit.ly/1alg2hy), the International Committee of Medical Journal Editors (ICMJE; (http://bit.ly/1rIp3Kg), and the Council of Science Editors (CSE; http://bit.ly/1Lmq3VX), among others—and we regard the reporting guidelines listed here as part of that process. We are therefore encouraging authors to seek appropriate guidelines for their submitted studies, fill in the available checklists, upload those checklists with your manuscript at submission, and list in the cover letter which guidelines were followed in producing your manuscript. We will be asking our editors and reviewers to look over these checklists, when included, as part of the review process.

Adhering to published guidelines will be seen as a positive factor by both the editorial staff and external reviewers when your manuscript is reviewed. Thus, it is in your own best interest, as well as that of the journal and the broader research community, to consider using established checklists…a win-win-win situation!

Based on the types of studies that *GIM* publishes, the following is a list of guidelines that we have identified as being relevant. However, we encourage potential authors to seek established guidelines and checklists that they judge to best represent the methods used in their own research.

We sincerely thank you in helping us keep the articles published in *GIM* at the very highest level of scholarship. *—Jan Higgins, Managing Editor, and James P. Evans, Editor-in-Chief*

Please note the list below is not exhaustive; we refer you to the National Library of Medicine's Research Reporting Guidelines and Initiatives (http://1.usa.gov/1WsKiwN) and EQUATOR (http://bit.ly/1TRWp2r) for a more complete set. The online version of this article has clickable links below; for print readers, URLs for these guidelines can also be found at these two sites mentioned above.

- Consolidated Health Economic Evaluation Reporting Standards Statement (CHEERS; http://bit.ly/1s2vmbd)
- ACMG standards and guidelines for the interpretation of sequence variants (http://bit.ly/1YoqGqM)
- ACMG policy statement on analysis and reporting of secondary findings in clinical genome-scale sequencing (http://bit.ly/1Tdnv42)
- ACMG standards and guidelines for the interpretation and reporting of postnatal constitutional copy number variants (http://bit.ly/1UWF0rC)
- Strengthening the Reporting of Genetic Association Studies (STREGA): An Extension of the STROBE Statement (http://bit.ly/1ZKeBfO)
- Standardized Human Pedigree Nomenclature: Update and Assessment of the Recommendations of the National Society of Genetic Counselors (http://bit.ly/1vG3ZOo)
- Human Genome Variation Society nomenclature for gene variations and guidelines on variation databases (http://bit.ly/1Ns8ZGd)
- National Human Genome Research Institute: the Elements of Morphology Project: an introduction to standardized clinical nomenclature for dysmorphic features (http://1.usa.gov/1T9fH11)
- The HuGENet HuGE Review Handbook, version 1.0: guidelines for systematic review and meta-analysis of gene disease association studies (http://1.usa.gov/1T9fH11)
- FSI: Genetics: "Publication of population data for forensic purposes" (http://bit.ly/1XnAYsZ)
- AJMG: "Reporting genetic results in research studies: summary and recommendations of an NHLBI working group" (http://bit.ly/1s2Btwc)
- JNCI: "Gene expression-based prognostic signatures in lung cancer: ready for clinical use?" (http://bit.ly/1UWl0Ez)
- BJC: "REporting recommendations for tumour MARKer prognostic studies (REMARK)" (http://bit.ly/2168xOy)
- GIM: "Strengthening the reporting of Genetic RIsk Prediction Studies: the GRIPS Statement" (http://bit.ly/1T8AZzh)