NEWS BLOG

Patients should learn about secondary genetic risk factors, say recommendations

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Imagine getting a chest X-ray to identify the cause of a serious cough. The radiologist finds a shadow that wasn't causing the cough but could be a tumour. In many cases, it is obvious what to do upon uncovering these sorts of secondary or incidental findings — most doctors would follow up on the search for a possible lung tumour, for example.

But genomic information presents a special case: genes are predictive, but not perfectly so, making some results murky. And many genetic diseases and predispositions to disease don't have clear and obvious paths for clinical management, potentially making them a lifelong psychological burden.

Today, the American College of Medical Genetics and Genomics (AMCG) released recommendations for how genome-sequencing laboratories should report incidental findings after a doctor orders a full or partial genome sequence. It defines a minimum list of about 60 genes and 30 conditions that should be reported to the doctor as part of a patient's care, whether the patient wants to know them or not. But the guidelines stop far short of recommending that all risk factors be passed on to doctors and patients.

From gene variants that cause malignant hyperthermia susceptibility to the *BRCA1* and *BRCA2* variants associated with breast and ovarian cancers, there are some well-established links for conditions that can be managed or monitored clinically. The ACMG recommends treating children no differently from adults, and leaves the responsibility of passing the information on to patients to the ordering clinician. As with a suspicious shadow on an X-ray, "it is up to the ordering clinician to contextualize those findings," says Robert Green, a medical geneticist at Brigham and Women's Hospital in Boston, Massachusetts, and the co-chair of a working group that has been refining the recommendations for more than a year.

Few, if any, countries worldwide have developed such specific guidelines. "This is a pioneering effort," says Muin Khoury, who heads the office of public-health genomics at the US Centers for Disease Control and Prevention in Atlanta, Georgia. And there is a need.

The number of personal genomes ordered for clinical purposes to date is probably in the hundreds or thousands, but with the cost of genome sequencing dropping rapidly and the number of companies vying to interpret genome data rising, 'prescribing' genomes to patients could become a regular practice, and such recommendations may inform the standard of care.

Some argue that the recommendations are too conservative. A document describing them — released today at the annual meeting of the ACMG in Phoenix, Arizona — notes that the working group tried to strike a balance between what it calls genetic libertarians, "who feel that patients have the right to full and complete accounting of all possible risks," and genetic empiricists, who believe that data do not support most disease–gene associations and that "it is irresponsible to create the psychological burdens of being a 'patient in waiting.' "

Gholson Lyon, a geneticist at Cold Spring Harbor Laboratory in New York, says that the document is "biased heavily" in favour of the empiricists and restricts the ability to analyse the millions of genomes that could come online in the coming years and support research.

Nancy Spinner, chief of the division of genomic diagnostics at the Children's Hospital of Philadelphia in Pennsylvania, says that the recommendations are helpful and thoughtful on the complexities of the situation, even though they differ in some ways from her own team's practice. Her team does not give back results for children if the risk factor is for adult-onset conditions. "We have a little more of a conservative approach," she says.

The recommendations pertain only to clinical sequencing and not to research or sequencing for healthy people. Also, says Green, they are a work in progress. The list of genes and disorders may expand or contract on the basis of how clinicians and patients respond. "We tried to imagine a world in which a lot more people are going to be sequenced. I don't know if we've gotten it right, but I believe we've put a lot of effort into a reasonable first step."

The headline of this story has been changed to reflect the fact that ACMG has issued recommendations, not guidelines.

Previous post
Investigation clears US interior-department staff of misconduct

Next post
Internet billionaire throws lavish soiree for physicists

Comments

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Gholson Lyon said: Due to the fact that I am quoted above, I want to provide the audience with my entire quote, so that they understand the way this was worded in my email to the reporter, Brendan:

Comment on ACMG guidelines on the return of secondary findings, issued March 21, 2013

The ACMG guidelines on the return of secondary findings is a very conservative set of recommendations. They state that they are attempting "to strike a balance between the positions of genetic libertarians and the genetic empiricists, guided by the currently available scientific literature, clinical experience, the consensus of our Working Group

members and the traditions of clinical medicine."

But, this report is biased heavily in favor of the genetic empiricists, as they are suggesting that results be returned for about 60 genes, out of an approximate total of 20,000 protein-coding genes in the human genome, not to mention the thousands of other identified, important noncoding elements of the genome! There are 6 billion nucleotides of DNA in every cell of the human body, and there are 25-100 trillion cells in each human body. Given somatic mosaicism, epigenetic changes, and environmental differences, no two human beings are the same, and therefore the expressivity of any mutation will be different in each person.

Therefore, how we will ever get to a world of millions of whole genomes shared and analyzed for numerous additive, epistatic interactions and gene X environment interactions, so that we can make any reliable predictions for any one human being, if we are only recommending return of results from ~56 genes? We need to sequence and collate the raw data from thousands and then millions of exomes and genomes, so that we can actually begin to really understand the expressivity patterns of any mutation in the human genome in any one person. The report does not even cite any of the revolutionary and disruptive work by genetic libertarians, including that of 23andMe and the Personal Genome Project. Some representative papers are below. This material is also discussed in the review in Genome Medicine that I published last year.

Dealing with the unexpected: consumer responses to direct-access BRCA mutation testing
Uta Francke 1,2, Cheri Dijamco1, Amy K. Kiefer1, Nicholas Eriksson1, Bianca Moiseff1, Joyce Y. Tung1, Joanna L. Mountain1

https://peerj.com/articles/8/

A public resource facilitating clinical use of genomes.
Ball MP, Thakuria JV, Zaranek AW, Clegg T, Rosenbaum AM, Wu X, Angrist M, Bhak J, Bobe J, Callow MJ, Cano C, Chou MF, Chung WK, Douglas SM, Estep PW, Gore A, Hulick P, Labarga A, Lee JH, Lunshof JE, Kim BC, Kim JI, Li Z, Murray MF, Nilsen GB, Peters BA, Raman AM, Rienhoff HY, Robasky K, Wheeler MT, Vandewege W, Vorhaus DB, Yang JL, Yang L, Aach J, Ashley EA, Drmanac R, Kim SJ, Li JB, Peshkin L, Seidman CE, Seo JS, Zhang K, Rehm HL, Church GM.
Proc Natl Acad Sci U S A. 2012 Jul 24;109(30):11920-7. doi: 10.1073/pnas.1201904109. Epub 2012 Jul 13.
PMID:22797899

Efficient replication of over 180 genetic associations with self-reported medical data.
Tung JY, Do CB, Hinds DA, Kiefer AK, Macpherson JM, Chowdry AB, Francke U, Naughton BT, Mountain JL, Wojcicki A, Eriksson N.
PLoS One. 2011;6(8):e23473. doi: 10.1371/journal.pone.0023473. Epub 2011 Aug 17.
PMID:21858135

Comparison of family history and SNPs for predicting risk of complex disease.
Do CB, Hinds DA, Francke U, Eriksson N.
PLoS Genet. 2012;8(10):e1002973. doi: 10.1371/journal.pgen.1002973. Epub 2012 Oct 11.
PMID:23071447

Web-based genome-wide association study identifies two novel loci and a substantial genetic component for

Parkinson's disease.
Do CB, Tung JY, Dorfman E, Kiefer AK, Drabant EM, Francke U, Mountain JL, Goldman SM, Tanner CM, Langston JW, Wojcicki A, Eriksson N.
PLoS Genet. 2011 Jun;7(6):e1002141. doi: 10.1371/journal.pgen.1002141. Epub 2011 Jun 23.
PMID:21738487

Identifying disease mutations in genomic medicine settings: current challenges and how to accelerate progress.
Gholson J Lyon and Kai Wang, Genome Medicine 2012, 4:58 doi:10.1186/gm359