How will genomics enter day-to-day medicine?

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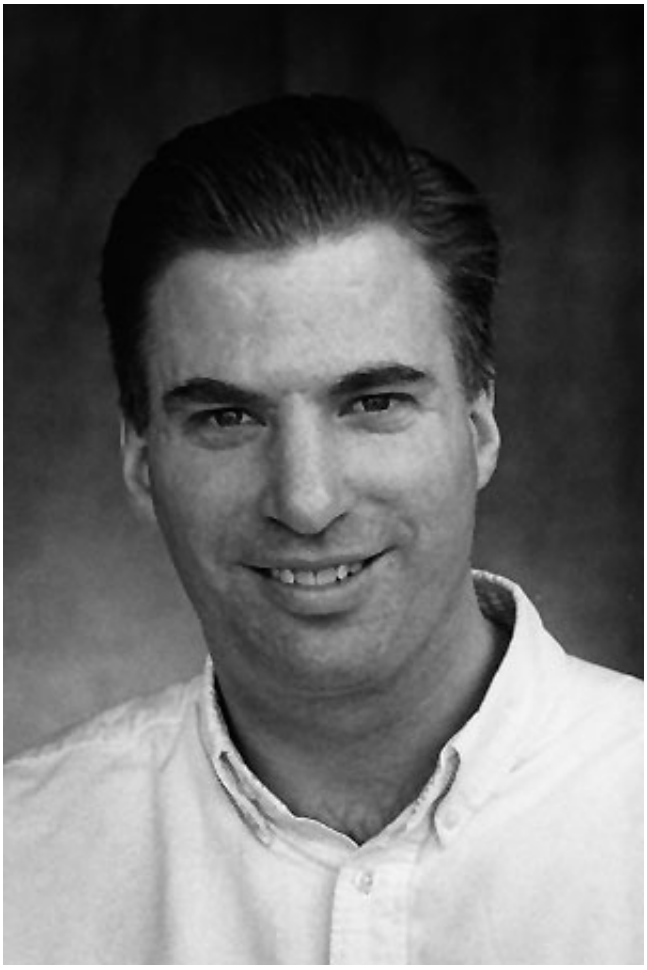

Ian D. Krantz, M.D., is the director of the Individualized Medical Genetics Center at The Children's Hospital of Philadelphia. Credit: The Children's Hospital of Philadelphia

A quiet transformation has been brewing in medicine, as large-scale DNA results become increasingly available to patients and healthcare providers. Amid a cascade of data, physicians, counselors and families are sorting out how to better understand and use this information in making health care decisions.

National experts who have gathered in Clinical Genetics Think Tank meetings at two large pediatric hospitals recently issued their first recommendations for integrating genomics into clinical practice.

The recommendations appeared online May 12, 2016 in *Genetics in Medicine*, co-led by Ian D. Krantz, M.D., director of the Individualized Medical Genetics Center at The Children's Hospital of Philadelphia (CHOP), and Ronald D. Cohn, M.D., co-director of the Centre for Genetic Medicine at the Hospital for Sick Kids in Toronto.

"As genetic testing has become more complex, it's being applied across many more medical specialties and into primary care," said Krantz, a clinical geneticist. "These tests will move toward broad use in screening healthy populations, and our recommendations aim to help people better integrate testing results into clinical practice."

Krantz and co-author Sarah Bowdin, M.D., of the Centre for Genetic Medicine at the Hospital for Sick Kids in Toronto, spearheaded the two Clinical Genetics Think Tanks, hosted at their respective hospitals in 2014 and 2015.

Co-authors of the recommendations are other Think Tank participants: clinical geneticists, genetic counselors, and laboratory professionals and bioinformatics experts. "Our co-authors represent the main stakeholders in this field," said Krantz. "We also included patients and parents in the Think Tanks, to incorporate their experiences in dealing with these concerns on an everyday basis."

Krantz added that he and Bowdin launched the Think Tanks after hearing from colleagues struggling with many similar issues as other institutions established clinical genomic and exome sequencing programs. Among those challenges were how to best interpret DNA findings, how to report to patients and clinicians about gene variants of uncertain significance, how to report secondary findings unrelated to the primary reason for the testing, and how to share findings with other centers. "As each institution independently developed its own procedures, we thought that exchanging experiences across our field could improve overall practice."

The recommendations address the pretesting process (including selecting patients and obtaining insurance coverage), patient and clinician education, interpreting sequence data, and posttest patient care (including how to return test findings and offer reevaluation of data). Another broad area, added Krantz, is phenotyping—establishing consistent terminology for patients' clinical characteristics, so that clinicians can better interpret the significance of DNA results, share data across centers, and ultimately standardize care for patients.

Krantz compared these new challenges to a more straightforward clinical situation—obtaining a targeted genetic test for fragile X syndrome—in which a test reveals whether a patient has a specific DNA change that causes fragile X symptoms. In contrast, current clinical genome and exome sequencing produces many unknowns: for each individual, test results yield many variants of uncertain significance, as well as secondary findings, which are genetic variants unrelated to the primary condition for which a patient is tested.

Facing a flood of DNA data, families told other Think Tank participants that they often preferred two posttest sessions to discuss test findings—one to learn the principal diagnostic results, and a second session to discuss secondary findings that are medically actionable.

Crucially, Krantz added, the data from genomic testing are dynamic—as new scientific knowledge accumulates, the significance of data changes: some findings of uncertain significance will become clearer, and will become medically actionable in the future, so that healthcare providers will need to devise ways to systematically offer future reevaluation of a patient's genome. "We need to make these data longitudinal, not static," he said.

One emerging issue raised in the Think Tanks is how to best integrate genomic results into each patient's electronic health record. This becomes all the more important, said Krantz, as clinical sequencing moves toward general screening of healthy patient populations, including newborns, as part of the progression toward precision medicine.

One conversation with a family, added Krantz, helped to drive home that issue. He was explaining results of genomic testing in a child with multiple medical issues. After learning the unexpected secondary finding that their child carried a cancer predisposition gene, the parents asked about performing the test for their healthy child too.

"We have framed this document not as a set of overt guidelines, but as recommendations, which we expect to change as our field evolves," said Krantz. He added that future Think Tanks may meet to address new challenges.

More information: Sarah Bowdin et al, Recommendations for the integration of genomics into clinical practice, *Genetics in Medicine* (2016). DOI: 10.1038/gim.2016.17

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