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WELCOME TO THE FESTIVAL

KEEPING IT IN THE FAMILY

Eric Green talks about his journey into science

A ROADMAP FOR GENOMIC MEDICINE

Find out what G2P are up to and the people making it all come together

LEADING THE WAY

Diana Bianchi talks all things prenatal testing

COMMENT

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THANK YOU GENOMIC MEDICINE – SOLVING THE INTERPRETIVE GAP

IF WE'RE CLEVER ENOUGH TO HAVE SEQUENCED OUR GENOME, THEN IS IT REALLY TOO MUCH TO FIND WAYS TO COOPERATE TO UNDERSTAND SEQUENCE VARIATIONS?

There is a fabulous video of a Rube Goldberg machine made of magnets and marbles (www.thisiscolossal.com/2016/05/ingenious-rube-goldberg-machines-built-from-magnets-and-marbles/). It is a good analogy for the complex landscape of genetic testing. The brilliant contraption reminds me of all the steps it takes for a genetic test to be thought of, selected, ordered, performed, covered by insurance, interpreted, and used in a care plan. However, there is an important difference. The magnet and marble machine is a contorted, nevertheless effective, path to a goal. Genetic testing sends marbles flailing out at every step and the goal of better health is not so assuredly attained. We all ought to try to do something about this together.

Like many others, I've embraced a reductionist approach to problem solving – I trained in biochemistry, practiced specialty medicine as a clinical and molecular geneticist, and now work in NIH's developer shop, NCBI. Walking through our building's conference center on the way to my office, I regularly see dozens of posters dissecting scientific questions into their lovely minutiae. Increasingly though, I feel queasy looking at the posters and wonder, how are we going to put Humpty-Dumpty back together again?

Most complex problems need to be teased apart. But here I'm going to call out what I believe are central problems in genomic medicine and suggest some solutions, while acknowledging that fixing one part at a time just won't work. Specifically, 1) we need physician engagement; 2) we must leverage clinical information for better test selection and interpretation; 3) we need to streamline test ordering and insurance steps; and 4) we must capture and share computable information – including clinical outcomes – globally and across the continuum of care. These problems are intertwined, so developing solutions will require many stakeholders to join under a very large tent. Taking a deep dive into one aspect of these imposing problems, as we do in our professional lives, just isn't enough. I'm hoping you will contribute to building a tent that fosters a comprehensive solution.

Let's start by looking at the current role of a physician (a non-geneticist) in genomic medicine. The patient is a young child with congenital heart malformations, specifically patent ductus arteriosus (PDA) and ventricular septal defect (VSD). The physician questions whether the patient has a specific syndrome, and the parents want to know what to expect for this child and for family planning. NCBI's MedGen has 79 conditions with the two clinical findings of PDA and VSD. The physician isn't sure how to refine the differential diagnosis, so they decide to order a panel for congenital heart disease and explain the testing plan to the family. They complete a mass of paperwork to determine whether the patient's insurance will cover the test, and fax the request. None of their time is reimbursed, and the chart work they regularly take home will cut deeper into their evening. The family has left the office long before it is known whether or not the test will be covered (and for how much), so the decision about whether to test is put off. The physician makes medical management decisions independently of any genetic test results. After putting more time into insurance appeals, the preauthorisation process is finalised, the test is run, and the lab collects the fee. The lab has found a missense variant in the TBX5 gene, which causes Holt-Oram syndrome (Heart-hand syndrome). ClinVar has data on the same variant from a single submitter (review status of one star), interpreted as a variant of uncertain significance (VUS). Adding insult to injury, the clinician gets a report of VUS. Thanks a lot, genomic medicine. This doctor won't repeat the mistake of ordering another genetic test anytime soon.

Now, let's look at the problem of genetic test interpretation – determining the pathogenicity of sequence variation. Genome interpretation is the grand challenge for medical science. As more sequence data are generated, the 'interpretive gap' in our understanding about the clinical significance

of variation grows wider. High-throughput and desktop sequencers will create an impressive pile of petabytes, but genome interpretation cannot be achieved without information about the phenotypes of sequenced individuals. (Even variant frequency data uses phenotype information in the form of demonstrably or presumably unaffected individuals.) The physician is needed to provide clinical correlation, which is crucial for interpretation because most variants don't come off the sequencing pipeline with a label of 'pathogenic' or 'benign'. But after the thankless experience of ordering a genetic test, we've already lost the physician at 'hello' and need to get them back in the tent.

Just how serious is this problem of variant interpretation? The 'clinical significance value' (figure 1a) is the submitter's interpretation of pathogenicity. ClinVar aggregates interpretations from different submitters about each variant. These interpretations often differ, so ClinVar provides a summary of conflicting interpretations. Examining these conflicts exposes today's interpretive gap. When the same variation is interpreted differently, we call that conflict a 'rank difference'. Rank differences of 2 or more can potentially change medical actions.

Of the 17,283 variants in ClinVar with conflicting interpretations by different submitters (as of 4/12/16), 26% have conflicts that are different enough to change clinical interpretation – that is, a rank difference of 2, 3, or 4 (figure 1b). This could mean the difference between placing an implantable defibrillator for a hereditary sudden death syndrome – or not – depending on which lab interprets the test results. The magnitude of current conflicts in variant interpretation, coupled with the consequences of misinterpretation, challenge whether or not we are ready for precision medicine.

It may seem surprising, but molecular genetics laboratories generally interpret variants without access to detailed phenotypes – by which I mean the clinical picture of symptoms, signs and test results that are the basis of clinical medicine. These so-called 'clinical findings' or 'clinical features' are the fabric of a diagnosis. In the case example, patent ductus arteriosus and ventricular septal defect are each clinical features. Of course, genetics practice and research entail deep phenotyping – the collection of detailed clinical findings – and many laboratories gather what phenotype information they can from clinicians. But most clinical sequencing is ordered by non-geneticists and little phenotype information is typically shared with the laboratory. The laboratory that interpreted the TBX5 missense variant as a VUS would likely be swayed toward an interpretation of 'pathogenic' if they learned the patient had any of the upper limb abnormalities that are part of Holt-Oram syndrome. But 'congenital heart disease' is generally the best they get on a requisition form. Even when individual patients lack distinctive findings, clinical data on small cohorts with the same variant can augment variant interpretation. Of course, data sharing among laboratories is necessary to aggregate clinical data for patients with the same variant, many of which are rare.

For well-described syndromes, variant interpretation becomes a more tractable problem by tuning the interpretation to the clinical picture. This is the same exercise that our radiology colleagues exhort us to do when they say 'clinical correlation is recommended'. But without access to clinical details, laboratories must rely on their private databases, any public variant databases, the literature, in silico tools, and possibly functional assays. Variant interpretation guidelines and data sharing smooth out the inconsistencies between labs, but the treasure trove of clinical information is mostly wasted.

I did a double-take when I realised that the ACMG guidelines for the interpretation of sequence variation provide little opportunity to use clinical findings. At best, such information is part of 'supporting' evidence and holds limited sway on the interpretation. Clinicians (and patients) do have clinical details, but seamless methods for capturing clinical phenotype and robust algorithms for variant interpretation need to be integrated into a genomic learning health system.

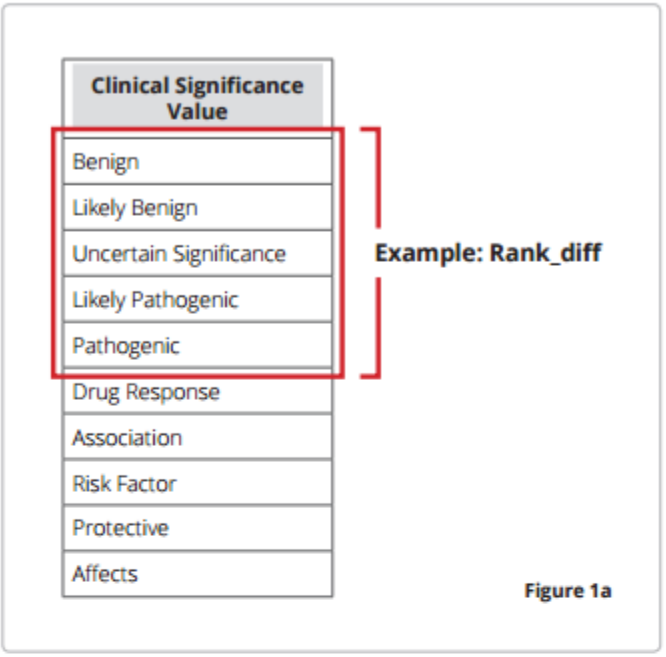

Figure 1a

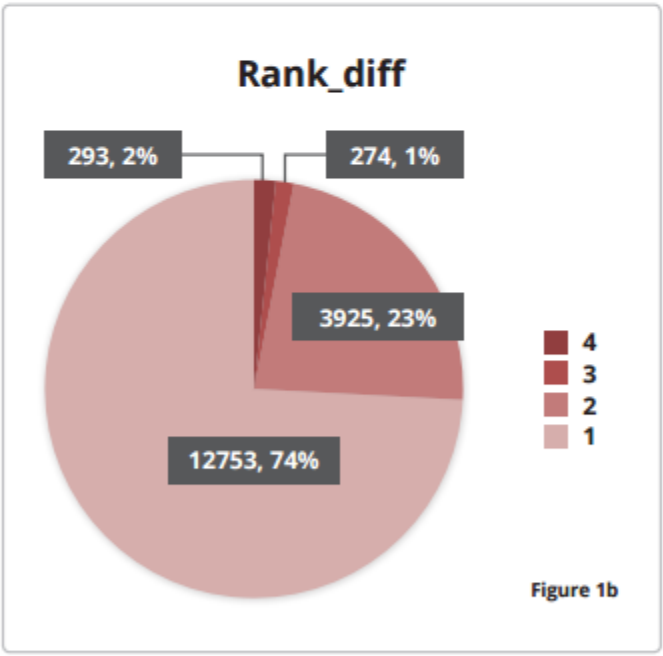

Figure 1b

To illustrate this, let's create a better pathway for the clinician to evaluate the child with congenital heart malformations. First, the patient has an insurance plan whereby they get negotiated discounts of the payer, so the full test cost is known. (Other insurance products can be imagined.) There is no delay in ordering the test but there are stipulations for coverage. The clinician needs to use a clinical decision support tool to enter the two findings - PDA and VSD - and is asked to add other pertinent findings from an upper limb examination (triphalangeal or absent thumb?). The differential diagnosis is narrowed and the gene list becomes smaller. →

Metabolic tests or x-rays may be a more efficient and cost-effective pathway to a diagnosis. Sanger DNA sequencing is performed on a smaller set of genes, at less expense than a next-generation sequencing gene panel, satisfying the payer and the family. The clinical features are used to populate a chart note and to support billing, and are also sent as computable phenotype codes to the laboratory. The physician dines with their family that evening.

To make things fair, let's end up with the same TBX5VUS result as before. This time, however, let's employ 'next generation phenotyping' and iterative data exchange by people and information systems. When the laboratory reviews the ClinVar entry – a VUS interpretation – they and the ordering physician go further as part of the new ecosystem. The laboratory uses a tool to annotate the test report with the clinical features of Holt-Oram syndrome, in a section labelled 'Clinical correlation recommended'. Following these recommendations, the physician finds no limb abnormalities upon examination, but hand x-rays reveal a carpal bone abnormality, supporting a diagnosis of Holt-Oram syndrome. The parents undergo echocardiography, ECG, and hand x-rays, molecular testing for the variant, and testing for maternity and paternity (as per the ACMG guidelines). Their parentage is established but neither has the variant or any phenotypic manifestations. The de novo mutation in the child, common in Holt-Oram syndrome, provides further supporting evidence for pathogenicity.

The laboratory receives information about the patient's carpal bone abnormality and the de novo origin of the variant. Following the ACMG rules for combining criteria to classify sequence variants, they issue a final genetic test report interpreting the variant as likely pathogenic. They submit their interpretation to ClinVar along with computable phenotype terms and parental results. Another lab eventually identifies the same variant in a patient, reviews the information in ClinVar, and adds to the pile of evidence. The community eventually triangulates upon the 'truth' about clinical significance – either pathogenic or benign – and there is one less VUS gumming up the engine of genomic medicine.

Meanwhile, the clinician tentatively uses the likely pathogenic interpretation by exercising a higher level of suspicion for cardiac conduction disease, and increases monitoring on the child. The family is told that if their child does indeed have Holt-Oram syndrome there should be no related intellectual disability. The risk that another child of theirs would have the condition is very low. The family finds others like themselves. Thank you, genomic medicine.

The ACMG guidelines state that in general, since patients already have phenotypes that prompt testing, these can be over-interpreted as evidence of variant pathogenicity (when they are actually red herrings). This is indeed a concern, and the reason why we need to use quantitative phenotype tools that are well-tuned to the genetic conditions under consideration. In silico predictive algorithms are integrated at all levels of the ACMG guidelines, yet validation of such tools for **clinical** applications very much remains a work in progress. Let's put more clinical data into the interpretation of **clinical** significance.

Like many others, I would like to help turn the great waste bins (ok, billing support systems) known as electronic health records (EHRs) into learning health systems that support genomic medicine. But unlike many who feel discouraged by the lack of time or basic interest on the part of physicians, I think clinician engagement can be attained.

We already have diagnostic tools for genetics that are modelled on pertinent positive and negative findings, the frequency of each finding in each disease and the timing of onset (and disappearance where relevant). No one need mention the word 'ontology', but clinicians' workflows must be respected. Software can be integrated into EHRs to support many desirable functions – selecting the best genetic (or other) test, populating a clinical note, and capturing computable clinical data for sharing. EHRs already integrate proprietary software for ICD-10 code selection; technology and usability are not true obstructions.

Failure to leverage clinical features into test ordering slants requests toward more expensive gene panels rather than less expensive tests for a few genes. For a condition with marked genetic heterogeneity, such as retinitis pigmentosa, a 50+ gene panel is most efficient. But panels containing extraneous genes that have little if anything to do with the clinical picture lead down more rabbit holes of variants to interpret. Is it any wonder why gene panels annoy the payers so much?

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To build solutions, we need a coalition of stakeholders to participate in the creation of a new data exchange 'utility', like a power utility which relies on an energy grid. No hospital system, medical professional organisation, payer, EHR vendor, or data management organisation can kindle this vision on their own. A high-stature convening organisation, possibly assisted by an industry facilitator, could provide the necessary activation energy to bring everyone under the tent. A consortium model, perhaps propelled by a request for proposals, would require several capabilities. These include: new insurance products; a test catalogue with firm prices; high volume capability for test order processing, prior approval and payment; expert phenotype and decision support tools that seed clinical and laboratory documentation; data capture and exchange to support variant interpretation and to aggregate clinical outcomes over time; collaboration with big pharma to adjudicate the relatively low cost of a one-time diagnostic test with the higher cost of continuous therapy; and a requirement to share variant interpretation and detailed supporting evidence with a public database. The database could become a resource for new research funding requests and for research parasites (those who perform rigorous secondary analysis of data, and play a key role in the scientific ecosystem!).

Is this over-reaching? Of course it is, but so are many great things that have actually been accomplished – think of the Human Genome Project. The Panama Canal now joins the Atlantic and Pacific Oceans, despite devastating yellow fever, malaria, and the original refusal of Colombia to agree to its construction. We may need another revolution of sorts to solve these epic problems. But if we are clever enough to sequence our species' genome, we ought to be able to cooperate with each other to interpret sequence variation for the good of every human being. ■

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