Published on *American Council on Science and Health* (https://www.acsh.org)

Is It Cancer or Is It Abnormal Cells? Explaining Risk

By Chuck Dinerstein — August 16, 2018

Courtesy of Wokandapix [1]

Two articles in the last few weeks caught my eye, the first, once again looking at predicting disease based on our genes, the modern-day equivalent to reading animal bones; the second a cautionary analysis of how labels frame our medical conversations. While they seem disparate, they are linked, are genome-wide studies clinically useful and if they are, what should we be telling or not telling our patients?

Genetic Predictions

The first study again delves into the UK Biobank, quickly becoming the go-to source of genome-wide association studies (GWAS) or polygenic scores. A brief refresher for those a little late to the party, GWAS look for genomic alterations to identify genomic segments associated with various diseases which can then be used to predict who might be at greater risk for developing a disease, like heart disease. The genetic associations are expressed as “polygenic scores.” The authors' goal is limited, to show that polygenic scores can identify at-risk populations for diseases in the same way that we have identified “rare monogenic mutations” diseases due to single mutations, like familial hypercholesterolemia [1]. Put another way can polygenic scores looking at our entire genome, identify at-risk groups and guide treatment in the same way BRCA mutations, a mutation of a single gene, help in breast cancer?

	Population at Risk			
	Disease	3-fold Increase	4-fold Increase	5-fold Increase	Predictive Valu
	Coronary artery disease	8%	2.3%	0.5%	81%

Atrial fibrillation	6.1%	1.5%	0.7%	77%	
	Type 2 Diabetes	3.5%	0.2%	0.05%	73%
	Inflammatory Bowel Disease	3.2%	0.8%	0.2%	63%
	Breast Cancer	1.5%	0.3%	0.1%	69%

*My use of the term predictive value represents the percentage of test cases identified by the polygenic scoring. E.g. For a population of 100 patients with type 2 diabetes, polygenic scoring would correctly identify 73% (true positive) and misidentify the remaining 27% (as false negatives)

First, let me point out that the researchers met their goal, polygenic scoring can identify at-risk populations, although not as well as some of our current surveillance. Mammography has a false negative rate of about 20%; the polygenic scoring has a false negative rate of 30%. But what is the clinical utility or value of polygenic scoring? How does it change care?

The unfortunate answer is that at this point, it does not. This risk scoring may focus surveillance, but it neither prevents or treats any of these problems. [2] The genomic profile is fixed at birth, so this information could be made available shortly after parents take their newborn home. The authors conclude:

> *"Risk communication will require serious communication…the usefulness of the knowledge and the potential harms to the individual may vary with the disease and stage of life…Yet, it may not be feasible or appropriate to withhold information that can be readily calculated from genetic data."*

Which brings us to our second study, using the C-word, Cancer.

What's in a word

The article itself is labeled an analysis, but it is more an opinion piece, thought-provoking, with 58 references, but few quantifiers, unless you count "may," "more," or "hundreds of cases" as quantities. There are some diseases that we classify as cancer that follow a very benign course, infrequently causing harm during one's lifetime. Among them are a form of thyroid cancer as well as a form of breast cancer, ductal carcinoma in situ (DCIS) and some prostate cancers.

The researchers point out that a patient given the diagnosis of any one of these cancers is apt to focus on the word cancer and ignore the rest of the conversation about low risk. As a result, many patients choose a treatment that allays their fears rather than active surveillance, where patients are followed more closely. Now in some instances, the watchful waiting we call active surveillance is equally safe but does little to quell anxiety. The authors note that active surveillance in prostate cancer “increases men’s level of anxiety, rates of depression and fear of cancer recurrence;” and 25% of them have surgery or radiotherapy anyway despite no evidence of disease progression.

The proposed fix - changing vocabulary, removing the “medicalized labels” [3] for softer terms like abnormal cells or lesions. No longer do we unnecessarily engender fear by saying you have a broken bone or greenstick fracture; now we could use the term “crack in the bone.” As both a lapsed surgeon and writer, I get it, words matter, especially as they frame discussions about prognosis and treatment. But am I alone in thinking that choosing these other terms is a throwback to more paternalistic times, you know, before patient-centered care, when doctors knew best, and patients were more childlike; before patient autonomy was a thing. They also see an additional benefit for the counseling clinician, making us “feel more comfortable recommending less invasive options to patients.” They conclude by stating

> *“Labels need to be biologically accurate, it also needs to be something patients can understand, and that will not induce disproportionate concern.”*

So there we have it. One study shows how polygenic scoring informs parents and their newborn of a three, four or five-fold “risk” of breast cancer or type 2 diabetes and another group tells us that our words may create unnecessary concern. Maybe we should tell the parents that their newborn has a four-fold risk of “sugar” or “abnormal cells,” that’s not as threatening, is it?

[1] This genetic mutation results in a metabolic “error” causing a two to three-fold increase in LDL cholesterol levels, associated with a 3-fold increase in coronary artery disease compared to patients without the mutation. It impacts 0.4% of the population.

[2] All GWAS studies are population specific. These results apply only to the UK population and “will not have optimal predictive power for other ethnic groups.” I would add that if genetics explains only a fraction of disease risk and that other environmental factors are involved, then the predictive power of these tests is also limited by the environment of these individuals.

[3] The use of medicalized in this context is puzzling, after all, we are talking about a medical diagnosis.

Sources: Genome-Wide Polygenic Scores for Common Diseases Identify Individuals with Risk Equivalent to Monogenic Mutations Nature Genetics DOI: 10.1038/s41588-018-0183-z

Renaming low-risk conditions labelled as cancer British Medical Journal DOI: 10.1136/bmj.k3322
