Study finds 'Precision Medicine' may not always be so precise

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Precision Medicine in oncology, where genetic testing is used to determine the best drugs to treat cancer patients, is not always so precise when applied to some of the world's more diverse populations, according to a study led by the Translational Genomics Research Institute (TGen), an affiliate of City of Hope, and the Keck School of Medicine of the University of Southern California (USC).

Precision Medicine in oncology is based upon identifying mutations that have turned normally healthy cells into tumor cells and where possible matching those to targeted therapies. There are two main approaches to identify those changes. Ideally, a patient's tumor, as well as normal tissue—usually from a blood sample—are sequenced to identify mutations specific to the tumor.

However, collecting normal tissue is not always possible or feasible, thus tumor-only sequencing is an alternative. One is then left with trying to distinguish normal genetic variation from the actual tumor mutations. In general, population databases are used to filter out genetic changes that are inherited rather than specific to the tumor.

Precision Medicine using this type of tumor-only approach, as a means of guiding therapeutic intervention, is more precise for those of European decent, and less precise for those whose ancestry is from Latin America, Africa and Asia, according to the study published online Oct. 19 in the scientific journal *BMC Medical Genomics*.

In an effort to help identify those genetic variants that might cause cancer when normal tissue is not available, the TGen-USC team devised a genomic tool with the Harry Potter-ish name of LumosVar. While this tool represents a significant improvement for research purposes, even this technological advance is not of sufficient precision to determine which anti-cancer drugs to give individual patients.

"The field of precision medicine isn't taking into account population differences. The approaches being used are imprecise when you look at very specific populations," said Dr. John Carpten, Director of the Institute of Translational Genomics at the Keck School of Medicine of USC, and one of the study's lead authors.

The problem is multi-pronged:

- Most of the tens of thousands of individuals worldwide who have undergone whole-genome sequencing—the spelling out of the nearly 3 billion chemical bases in their DNA—are of European decent, biasing existing databases used to exclude false-positive variants. There is a need to sample more people from more diverse parts of the world.
- European ancestry turns out to be among the least diverse genetically, having the fewest genetic variants, especially individuals with roots in Scandinavia. Those whose ancestry is traced from less developed parts of the world—areas that have experienced the most rapid population increases over recent millennia—have the most genetic variants, with individuals originating from Bangladesh having among the world's most diverse genomes.
- Many hospitals collect tumor tissue for research purposes without collecting normal tissue for comparison. This is especially true in under-developed nations. Without these normal-cell samples, it is difficult to determine which mutations potentially cause cancer

and which are simply benign variants in the human genome.

"It is very difficult to identify a somatic, or potentially cancer-causing, variant when you don't have a germline, or normal, sample," said Dr. Rebecca Halperin, a TGen Assistant Research Professor and the study's other lead author. "It's even worse, depending on your ancestry. You get more false positives—those genetic variants that don't cause cancer—from populations with non-European ancestry."

To assist researchers in sorting out false positives, TGen and USC researchers devised a computational tool called LumosVar, a Harry Potter reference to Lumos (light) in the story's magic spells, and Var for genetic variance. LumosVar is essentially a tool to light up the genome's potentially cancer-causing genetic mutations.

"Simply sequencing more individuals from various populations is not enough. We really need access to the germlines. But when those aren't available, we need better tools and this is where we have put our focus," said Dr. David W. Craig, Vice Chair of the Keck School of Medicine of USC's Department of Translational Genomics and the study's senior author.

Drs. Craig and Halperin are the co-creators of LumosVar.

One surprising finding of the study involves the "out of Africa" theory of evolution; the fact that all modern humans across the globe can be genetically traced back to ancestors from Africa. Researchers assumed that because Africa was a starting point that those with African ancestry would be more genetically diverse, and those populations who spread elsewhere across the globe would, as descendants of more recent common ancestors, became less genetically diverse. Instead, rapid population expansion in Africa, as in South America and Asia, over millennia has been the driving force resulting in more genetically diverse

individuals.

"The added complexity of identifying inherited genetic changes surprised me and many others we have shared these findings with," said Dr. Craig, who also is a Professor and Co-Director of the Institute of Translational Genomics at the Keck School of Medicine of USC.

"There is a growing body of knowledge on the shortfalls of Precision Medicine," said Dr. Rick Kittles, Professor and Founding Director of the Division of Health Equities, Department of Population Sciences, at City of Hope, and one of world's foremost scientists in the area of population genetics and cancer.

"This study goes beyond the barriers to participation and provides insight on the lack of genetic data from diverse populations and its impact on the value and utility of Precision Medicine. There is still much work to be done in order for all communities to benefit from Precision Medicine," said Dr. Kittles, who was not part of the study, but was asked by the authors to provide perspective on the study's findings.

The problem is not trivial or academic. Patients whose tumor-cell sequencing cannot be matched with their normal-cell sequencing, run the risk of being misdiagnosed, researchers said.

"That means you might be getting the wrong therapy simply because of our lack of understanding of the genetic architecture based on one's ancestry," Dr. Craig said. "These findings argue that we're really not doing a very good job of doing Precision Medicine for many populations."

Dr. Carpten added, "Tumor-only sequencing in patients from populations that have undergone rapid expansion significantly decreases the precision of Precision Medicine. Importantly, the greater impact will

be on individuals from underrepresented communities."

Even for those of European ancestry, the lack of normal-cell sequencing to compare to tumor-cell sequencing still poses substantial risk, the study says: "Even within a European ancestry cohort, there are many individuals who still will have a high number of private variants that would result in a higher number of false positives."

Still, the study points to the LumosVar, which the TGen-USC team has offered as an open-source tool for any researcher to use, as a substantial improvement in searching for potentially cancer-causing mutations.

"While the goal of the present study was to evaluate the benefit and limitations of leveraging allele frequencies to distinguish somatic and germline variants in unmatched tumor samples, in the process we have developed a tool that we have made available to the research community," the study says.

"We have clearly demonstrated that LumosVar has improved positive predictive value in calling somatic variants compared to database filtering, which is the most commonly used approach with unmatched tumor samples," the study says. "When analyzing archival samples in a research setting, we believe LumosVar would be of great utility."

The study—titled: A method to reduce ancestry related germline false positives in tumor only somatic variant calling—predicts that, as the cost of high-depth sequencing continues to decline, the sensitivity of tools like LumosVar will continue to improve.

More information: Rebecca F. Halperin et al, A method to reduce ancestry related germline false positives in tumor only somatic variant calling, *BMC Medical Genomics* (2017). DOI: 10.1186/s12920-017-0296-8