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Inherited Susceptibility to Pancreatic Cancer in the Era of Next-Generation Sequencing

See "Prevalence of germline mutations in cancer predisposition genes in patients with pancreatic cancer," by Grant RC, Selander I, Connor AA, et al, on page 556.

This issue of *Gastroenterology* presents a manuscript from Ontario, Canada by Grant et al.[1] The study provides early insights into the prevalence of point mutations and small insertions and deletions for a set of 13 well-characterized cancer predisposition genes. The genes they tested using a multigene panel include *APC*, *ATM*, *BRCA1*, *BRCA2*, *CDKN2A*, *MLH1*, *MSH2*, *MSH6*, *PALB2*, *PMS2*, *PRSS1*, *STK11*, and *TP53*. They sampled 290 patients from a population-based cohort of patients with histopathologically confirmed pancreatic ductal adenocarcinoma (PC), who were further grouped based on family history.

They detected eleven germline mutations in 7 genes (*ATM*, *BRCA1*, *BRCA2*, *MLH1*, *MSH2*, *MSH6*, and *TP53*), the majority associated with inherited breast and colorectal cancer risk. The overall mutation carrier prevalence was 3.8%, increasing to almost 10% when the proband or a first-degree relative had a history of breast or colorectal cancer. Family history of PC, younger age at diagnosis, and stage were not associated with mutations in the genes sequenced. Although probands with a personal or family history of breast or colorectal cancer were most likely to carry mutations, personal and family history of cancers associated with mutations in relevant specific genes were absent in several cases. Fewer than one-half of those who tested positive in the study satisfied current criteria for genetic testing based on clinical characteristics, implying that more than one-half would not have been detected within our current clinical framework.[2] Although some misses may be related to the reliability of family history, a higher than expected prevalence of germline mutations in cancer predisposition genes is also reported in other cancer types, such *BRCA* mutations in "sporadic" triple-negative breast cancer.[3]

This assessment of a number of well-known cancer predisposition genes in a broader context, compared with testing in patients with a clinically high risk of carrier status, raises significant questions concerning our understanding of the molecular pathology of PC predisposition. It also begins to paint a picture of the challenges ahead to our understanding of inherited cancer risk and the implications for current clinical approaches as genomic sequencing becomes broadly available.

Our traditional approach to understanding cancer predisposition emerged because of limitations in our ability to sequence individual genes, let alone exomes or genomes. This allowed us to define a number of highly penetrant genes, with significant improvements in clinical management. More recently, next-generation sequencing approaches have accelerated discovery through genome-wide linkage analysis in such highly penetrant families. In addition, genome-wide association studies have identified candidate predisposition loci, but mostly with small effect sizes. Currently, there are 114 recognized cancer predisposition genes (reviewed by Rahman[4]). The pragmatic reality of only testing those with a high risk of developing a malignancy has generated an acquisition bias to our understanding of cancer predisposition today. This "forward genetics" approach has served us well for many years, yet has instilled a dogma that may limit progress in the emerging "reverse genetics" era. Challenges have completely shifted from the technological limitations of DNA sequencing, to the far greater challenge of understanding the biological basis of cancer predisposition and defining clinical validity and clinical utility, and then delivering an appropriate and viable benefit to the community.

The increasing ease with which genomic sequencing technology can be accessed for many clinical applications and perhaps for what can be called "curiosity" testing will pose significant challenges in the interpretation and application of the data generated. As the article points out, testing multiple, well-characterized cancer predisposition genes has immediate potential benefits when performed in the context of current clinical practice, but also presents challenges. We know the relative risk of developing a cancer in the setting of a family history. What we do not know is the risk of carriers without a family history. The data reported in the manuscript by Grant et al suggest that there are a significant number of mutation carriers in known cancer predisposition genes with pancreatic cancer that do not have a family history. Case-control and other traditional studies are required to define the relative risk of such individuals and their family members, but may be intractable. Moreover,

inherited pancreatic cancer may also have specific characteristics. There are several familial syndromes that are characterized predominantly by cancers of other organs, which are also associated with pancreatic cancer and account for 15%–20% of familial pancreatic cancer. These include hereditary breast ovarian cancer, Peutz-Jegher syndrome, familial atypical multiple mole melanoma, Li–Fraumeni syndrome, hereditary nonpolyposis colorectal cancer, and familial adenomatous polyposis. Patients with familial pancreatic cancer who are not within these syndromes are also associated with an increased incidence of extrapancreatic malignancies.[5] These factors point to a complex genetic predisposition pattern for pancreatic cancer and perhaps many other cancer types.[3,6] In some instances, the presence of a germline mutation also influences therapy. For example, early studies are demonstrating that *BRCA* mutations confer sensitivity to PARP inhibitors. This is particularly important for pancreatic cancer where current therapies are largely ineffective, and clinical trials are recruiting for the testing of novel therapies that target defects in DNA maintenance, offering patients attractive opportunities.

The substantial diversity of the human genome and the complexity of cancer genomes imply that our traditional approach to identifying predisposition genes and quantifying relative risk will require even larger numbers. We will be challenged by unraveling the contribution of multiple loci, including combinations of different genes, coexistent variants within genes, and gene–environment interactions. Moreover, we are only utilizing limited endpoints for cancer predisposition: increased incidence and young age of onset. We have yet to examine other endpoints, such as survival. Most genes we have identified have either well-known large effects such as Li–Fraumeni syndrome and *TP53* mutations, or those that occur early in carcinogenesis such as *APC* mutations. Inherited deleterious variants may not lower substantially the age of onset, or increase dramatically the incidence of a particular cancer, but may lead to a poor prognosis cancer because the initiating mutation is still environmentally determined, but "progressor" mutations may already be present.

To circumvent these hurdles, we need to identify other ways to gather the evidence required to impact on clinical management.[7] We can only estimate the likely extremely large cohort sizes we will need for case control studies, notwithstanding the challenge of defining low-risk controls. The concept of healthy controls of advanced age may be helpful, and requires assessment; however, it is likely that only large-scale "knowledge bank" approaches that track generations over time with well-documented clinical histories will begin to unravel this complexity. We also need to define the role of other measures such as functional readouts, or surrogate measures of the consequences of specific genomic variants, or constellations of variants to better understand cancer predisposition, and explore the potential direct clinical utility of such approaches. An example is using whole-genome sequences to identify surrogates of genetic defects in tumors. These defects include microsatellite instability and mutational signatures associated with defects in DNA maintenance. The latter is a specific signature of point mutations that are associated with defects in *BRCA1* and *BRCA2* function.[8] Variants associated with such surrogate measures can then focus experimental approaches to demonstrate the functional significance of these variants.

As we accumulate more cancer genomes through large-scale international efforts such as the International Cancer Genome Consortium[9] and The Cancer Genome Atlas,[10,11] the germline sequences that accompany these genomes will provide insights into the prevalence of known predisposition loci in the germline, and perhaps point to novel candidates.[12] These approaches will define hypotheses that could be tested using different methodologies and begin to define a framework for expanding the way we approach cancer predisposition. Other insights may be gleaned from a better understanding of precursor lesions, the mutations that are present within them, particularly surrogate measures such as point mutation signatures that could imply mechanisms operating during early carcinogenesis. Familial tumor registries such as the National Familial Pancreatic Cancer Tumour Registry at Johns Hopkins University,[13] with detailed data and biospecimen acquisition, provide an important resource for identification of candidate risk genes, clustering of related tumor types, the estimation of risk, and the assessment of early detection strategies. Follow-up and biospecimen acquisition (germline DNA, and where appropriate, tumor DNA) of patients and their families for index cases with variants of unknown significance may also bear fruit in the longer term.

In conclusion, the article by Grant et al presents some provocative findings, data that give us a taste of what lies ahead in understanding the biology of cancer predisposition, and the challenges of interpreting inherited genomic variants outside the traditional setting. This is of particular importance in highly aggressive cancers such as pancreatic cancer where the median survival is <6 months and the overall mortality is $>95\%$. The broad availability of genomic sequencing is inevitable and we need to be cautious in our interpretation of germline variants that are identified through this mechanism, particularly in the absence of family history. However, we need to be open to, and explore other ways of, defining variants that predispose to disease. Better quantifying the risk of disease in individuals, subgroups, and families is particularly important, because the most variable factor for intervention is likely to be the aggressiveness of a particular cancer type, the risks and benefits of the intervention required, the reliability of family history and an individual's philosophy, rather than the genetic variant, and its relative risk of acquiring the disease in a broad clinical context.

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Identifying Molecular Targets to Improve Immune Function in Alcoholic Hepatitis

See "Blockade of PD1 and TIM3 restores innate and adaptive immunity in patients with acute alcoholic hepatitis," by Markwick LJL, Riva A, Ryan JM, et al, on page 590.

Alcoholic liver disease (ALD) is a major cause of liver-related morbidity and mortality worldwide. ALD encompasses a range of disorders including steatosis, steatohepatitis, progressive fibrosis, cirrhosis, and hepatocellular carcinoma.[1] In addition, patients with underlying ALD (in most cases cirrhosis) and active drinking can develop an episode of acute-on-chronic liver failure named "alcoholic hepatitis" (AH).[2] AH in its severe forms bears a high short-term mortality. In these patients, liver homeostatic function is impaired profoundly and portal pressure is particularly high, leading to life-threating complications such as variceal bleeding, encephalopathy, and hepatorenal syndrome. Patients with severe AH are particularly prone to bacterial infections, reflecting intense derangement of immune function.[3] Although infections at admission often can be controlled with wide-spectrum antibiotics, the development of infections during hospitalization is linked to poor prognosis. In-hospital infections typically occur in patients with poor liver function, leading to systemic inflammatory response syndrome, and multiorgan failure. Therefore, targeted therapies aimed at improving immune function and preventing bacterial infections are clearly needed in this patient population.

In recent years, several studies have uncovered partially the mechanisms underlying the profound innate and adaptive immune disturbances in patients with AH. Paradoxically, these patients are characterized by both an