Genetic Risk Screening and the Usefulness of Whole Genome Sequencing (WGS)

Essentially all cancers are caused by acquired DNA mutations. Inherited cancer risk genes often act to increase a person's vulnerability to acquired mutations. During cell reproduction, DNA is duplicated and during this process errors in copying the code can occur. Fortunately, DNA repair-enzymes correct these base pair mis-matches and very few errors slip by. A mutation is an error that occurred during DNA copying that eluded correction. Unless a mutation occurs in a sex cell (sperm or egg) it is not heritable. Four possible outcomes can occur when a protein-producing gene becomes mutated: 1) the protein it produces can become more effective (a fortuitous event), 2) the protein's function can remain intact and unchanged (a "silent" mutation), 3) The protein's function can be partially diminished (a loss-of-function mutation), 4) the protein can become completely non-functional (a "null" mutation). When a DNA repair-protein is itself rendered less effective by a gene mutation, DNA copying errors will inevitably increase. Fortunately, mutations in only a small-subset of genes can contribute to cancer development. The most dangerous "driver mutations" occur in proto-oncogenes, tumor suppressor genes, and genes that repair DNA; as changes in these genes can caused unregulated cell growth. Studies have shown that most malignant transformations occurred after a cell acquired between 1 and 10 key "driver gene" mutations (the average number has been estimated to be 4-5 mutations). Fully transformed cancer cells often contain 60 or more total DNA mutations in "driver" and "non-driver" genes, and some cells show thousands of genomic alterations due to unusual genomic instability.

Up to 10% of all breast cancers can be attributed directly to hereditary causes; the most well known of which are the BRCA1 and 2 mutations. BRCA1 Protein, produced by the BRCA1 gene, acts as a tumor suppressor to stop cells from dividing out of control. BRCA2 Protein work to fix double-stranded DNA breaks that damage genes. These inherited mutations can increase a woman's lifetime risk for breast cancer to greater than 60%, yet up to 97% of women who carry the genes are unaware.

Lynch syndrome is the most common inherited cause of colon and endometrial cancer. Women who have Lynch syndrome have a 40% to 60% lifetime risk of developing endometrial cancer and a 10% to 12% risk of ovarian cancer. Lifetime colon cancer risk for Lunch syndrome is 20% to 74% for men and 20% to 52% for women. Early identification of Lynch syndrome can help manage cancer risk and significantly alters the routine monitoring recommendations that were developed for the low-risk general population. As many as 1 in 370 people have Lynch syndrome, yet 95% of them do not know they are at high risk for cancer.

Even among those with a personal history of cancer, a study of >1.36M patients diagnosed with cancer between 2013-2019 revealed that only 6.8% had hereditary cancer testing within 2 years of their diagnosis.

Most genetic mutations are triggered by environmental factors. An individual's lifestyle choices directly affects their risk of mutations. The list of potentially cancer-fostering lifestyle choices is large, and numerous factors can impact the risk of developing more than 100 types of cancer. For example, smoking, heavy alcohol consumption, failure to maintain a proper body mass index (BMI), sedentary lifestyles and poor nutrition all increase the risk for cancers. Everyone knows someone who has engaged in "bad" unhealthy habits like smoking yet lived well into their 90's without developing cancer. These people are often viewed as "lucky" but in truth, their luck often resides in the absence of inherited cancer causing genes.

While the exact number of cancer-associated genes is evolving (new genes are frequently being identified), at least 10–12 genes are currently recognized as having a well-established role in breast cancer susceptibility and several commercial Laboratories like "Natera", "Illumina", "Qiagen" and "Caris", offer testing panels containing these genes. In addition, some Testing Companies also offer expanded panels for genes that are possibly associated with other cancer risks *these genes are often referred to as gene "variants of uncertain significance" (VUS). For example, Natera's "Comprehensive Cancer Gene Panel" currently includes testing for the 7 "certain" cancer risk genes (2 BRCA and 5 Lynch Syndrome genes) but also includes 78 other "possibly associated" VUS cancer-risk genes. At one time in the past, the BRCA genes were classified as genes of "uncertain significance" however, as science advanced and clinical data accumulated, their role in causing cancers became more "certain". It should be expected that as more and more people with cancer are genetically tested, more and more cancer-associated-genes will be identified and moved from the "uncertain" risk classification into the "certain" category.

As new cancer-associated genes become identified, those desiring to know if they carry these genes will need to be re-tested with updated panels. This is a financial boon for Commercial Testing Companies offering the "Expanded" testing panels, but it is a financial burden for consumers and Medical Insurers, who will need to foot the bill for each subsequent re-testing. The solution for this problem of "gene testing-panel obsolesce" is Whole Genome Sequencing (WGS).

Estimates suggest that each of our cells carries 20,000–25,000 protein-coding genes; the "blueprints" for making proteins however, these genes represent only 1–2% of the human genome. The remaining 98–99% of our DNA is considered "non-coding", because it doesn't directly code for proteins; yet, these expansive non-coding DNA regions are far from non-functional; and includes important regulatory elements (e.g. gene promoters, suppressors and enhancers) that control when genes are active and how much of a protein is made. Therefore, the actual number of "functionally important" DNA elements in a human genome is probably closer to 30,000. **Whole Genome Sequencing** identifies every DNA sequence present in all 46 chromosomes in both the "coding" and "non-coding regions"; ***WGS is a "once-and-done" test that will never need to be repeated and will never become obsolete***. Although WGS provides limited information concerning gene methylations or mosaicism and often cannot assign "cis" or "trans" designations when 2 genetic variants exist within the same gene, its ability to detect the presence of "new" cancer-associated gene in a WGS code is not a limitation. As "new" pathological genes are identified, computer AI-driven "apps" can simply

re-scan a WGS file looking for a DNA code that matches the sequence of any suspected gene target.

There are several companies that use FDA-approved sequencing techniques such as LabCorp (In Vitae) and GeneDx but they offer WGS only for complex genetic conditions such as advanced cancer tracking, specialized pediatric/rare disease diagnostics, and prenatal screening with multimodal analysis such as RNA-Seq, structural variant analysis, STRs, mtDNA, UPD and DNA-methylation. It is nearly impossible to get Medical Insurance Companies to authorize payment for genetic testing without a very limited scope of investigation and a scientifically justifiable purpose. With a carefully worded "prior-authorization request", most Insurances will agree to pay for a limited genetic testing panel if the reason for testing meets their narrowly defined criteria for "Medical Necessity". If approved, testing is typically authorized to look only at the genes that would confirm a Physician's specific presumptive diagnosis or to provide additional information on a patient's proven diagnosis (like cancer). Most importantly, if your Insurance pays for the genetic testing, they have the right to view this information and to potentially make future coverage decisions for you based on any identified findings.

Because Genetic Testing Companies bill Insurers astronomically inflated prices for their services, your Insurer will often fight to the death to deny your genetic testing request. ***Based on your specific insurance policy, Natera and other Genetic testing companies can generate an automated bill detailing your "explanation of benefits" before genetic testing is done. Not uncommonly, this will show thousands of dollars of patient-responsibility and if a Lab submits this bills to the patient's Insurer, the patients will typically be responsible for any uncovered cost. In many situation, paying for genetic testing "out-of-pocket" is a cost saving option. If your Insurance rejects your Physician's prior authorization submission, or with approved Insurance coverage your cost-share responsibility of the billing is insanely high (due to a high co-insurance requirement or a high unpaid deductible), you can call Natera's billing department directly to request for a switch to their cash/self-pay rate (usually about $250 for most genetic panels) or apply for their financial assistance program. Keep in mind that these self-pay discounts are usually only applicable to small limited and specific gene panels, such as those targeting genes in a cancer risk panel or a kidney disease panel.

One important consideration is that for $150 dollars more (about $400 total), you can: 1) bypass your physician's inability to secure a prior authorization for WGS genetic testing, 2) bypass the aggravation that comes from fighting with your Medical Insurance Company when they inevitably deny payment for your "pre-approved" genetic testing, 3) obtain useful information from WGS that encompasses a multitude of health-related genes, 4) protect your WGS information from access by Medical Insurers and 5) obtain a useful DNA testing result that will never become obsolete.

Summary:

When it comes to recommendations for Preventive Health, Insurance Companies generally follow National Guidelines for Preventive Care ***and they assume that everyone has the same disease risk factors***. Knowing your individual genetic predisposition for specific diseases allows your PCP to justify more frequent evaluations and necessary treatments to help mitigate identified risks. With the advent of WGS "home testing" for under $400, medically savvy patients are seeking to incorporate genetic information into their medical care and will be looking to their over-whelmed PCPs for implementation guidance.

Because most PCPs are too busy to effectively integrate genetic information into Preventive Health plans, the first adopters of this technological advancement will likely be the "Concierge" Physicians; who have intentionally limited their practice size to improve patient access and increase face-to-face time. Unfortunately, one current road-block to "precision medical care", is the denial of Insurance coverage for WGS testing when the sole purpose is for planning Multi-system Preventive Health Care before a disease is detected. Although "personalized" Preventive Health plans based on an individual's genetics have yet to become "main-stream", future physicians will undoubted look back at this present time as the "dark ages" of "pre-genetic" medicine, akin to how we look-back in history and view the practice of "blood-letting" to remove "bad humors".