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Chapter

Genetic Contributors to Hereditary Cancer Predispositions: Do We Have Enough Information?

Tom Nolis and Rodney J. Scott

Abstract

Genomics medicine and molecular genetics are experiencing a surge of interest as well as a push for a more prominent role in mainstream medicine. This, coupled with the advancement of next-generation sequencing, along with a national, if not global, steering of funding to support the advancement and development of genetics is suggesting that we are entering a new age of medicine. As this push begins to gain some momentum, the impact of genomics medicine on clinical utility and the influence of supporting data on genes that make their way from research to diagnostic medicine are worth reviewing.

Keywords: genetics, genomics, utility, cancer, *BRCA1*, *BRCA2*, *PALB2*, population, family, epidemiology, multigene, panels

1. Introduction

One of the most fundamental clinical validity and clinical utility questions currently at the forefront of molecular genetic testing is as important today as it was nearly 30 years ago, "is the genetic variation detectable in the genes of interest actually associated with a clear and quantifiable risk for disease?" or in other words, "are the variants that we are finding in these genes relevant for the disease of interest?"

The question above is a very important one, and to be able to answer, it we must take a step back and explore clinical utility and epidemiology in genetics more thoroughly. The answer to this question requires an inevitable focus on cancer genetics as breast and ovarian cancer are excellent examples of both past and present accomplishments in genomics medicine. These disease entities are topical and have enough data to appropriately highlight the genetic journey previously taken into genomics medicine, and they are also able to shed light on how new genetic players are entering the diagnostic scene (e.g., *PALB2*).

Finally, the following text will briefly compare and contrast the significant influence of family-based and population studies on genetic data. This chapter will close on a more general note by reviewing the current cancer assessment guidelines and how these reflect the current clinical utility of genomics medicine.

1.1 Key points

- Clinical utility in genetics is largely a continual revamp of the ACCE framework.

- Genetic epidemiology has followed a natural flow paralleling the advancement of technology and detection.

- Family-based studies and population data are still at the forefront of both research genetics and diagnostic genomics.

- *BRCA1* and *BRCA2* are excellent models for useful genetics input.

  ○ This has led to a complete change in the identification and treatment of a very tangible cancer entity.

- Less penetrant genes in breast and ovarian cancer, such as *PALB2*, along with multigene panels have their place in genomics medicine, but, generally, quality supportive data are lacking.

2. Clinical utility in genetic testing

Clinical utility is a broad concept and one that is deeply fundamental in the world of medicine. At its most basic level, it is the essence of what propels medical advancement. It answers the question of "what should I do next?" when this question is asked by physicians, but it can also be a much larger almost all encompassing concept; as if to ask, "what is worth doing next?" in any field of medicine. Clinical utility, by many sources, can be simply defined as "the balance of benefits to risks" or more broadly refer to any use of test results to inform clinical decision-making [1]. A genetic test can be defined as a "test that involves the analysis of chromosomes, deoxyribonucleic acid (DNA), ribonucleic acid (RNA), genes, or gene products (e.g., enzymes and other proteins) to detect heritable or somatic variations related to disease or health. Whether a laboratory method is considered a genetic test also depends on the intended use, claim or purpose of a test" [2].

In some fields, such as in colorectal surgery, it is easy to determine clinical utility: if the patient's morbidity or mortality is improved by removing a tumor, then you remove it; otherwise you do not. In the realm of genetic testing, the concept of clinical utility can be difficult to precisely define—or even quantify. Indeed, this was reinforced when experts in evidence-based medicine and genetics for the Centers for Disease Control and Prevention (CDC) in 2005 failed to come to a consensus on the term "clinical utility" despite initially claiming to be confident in its meaning beforehand [1]. As a consequence, the term had to be elaborated on by the Analytic validity, Clinical validity, Clinical utility, and Ethical, legal and social implications (ACCE) project that was carried out by the Foundation for Blood Research with support from the CDC [1]. In screening or in diagnostic testing, clinical utility broadly refers to the ability of a test to prevent or ameliorate adverse health outcomes such as mortality, morbidity, or disability through the adoption of efficacious treatments conditioned on test results (**Figure 1**) [1]. The perceived value of genotypic information, at this point in time, includes a more thorough understanding of a patient's diagnosis, prognosis, risk, and disease or treatment susceptibility; the caveat is that this knowledge may not influence clinical management at all. Clinical utility in the ACCE framework was expanded to include
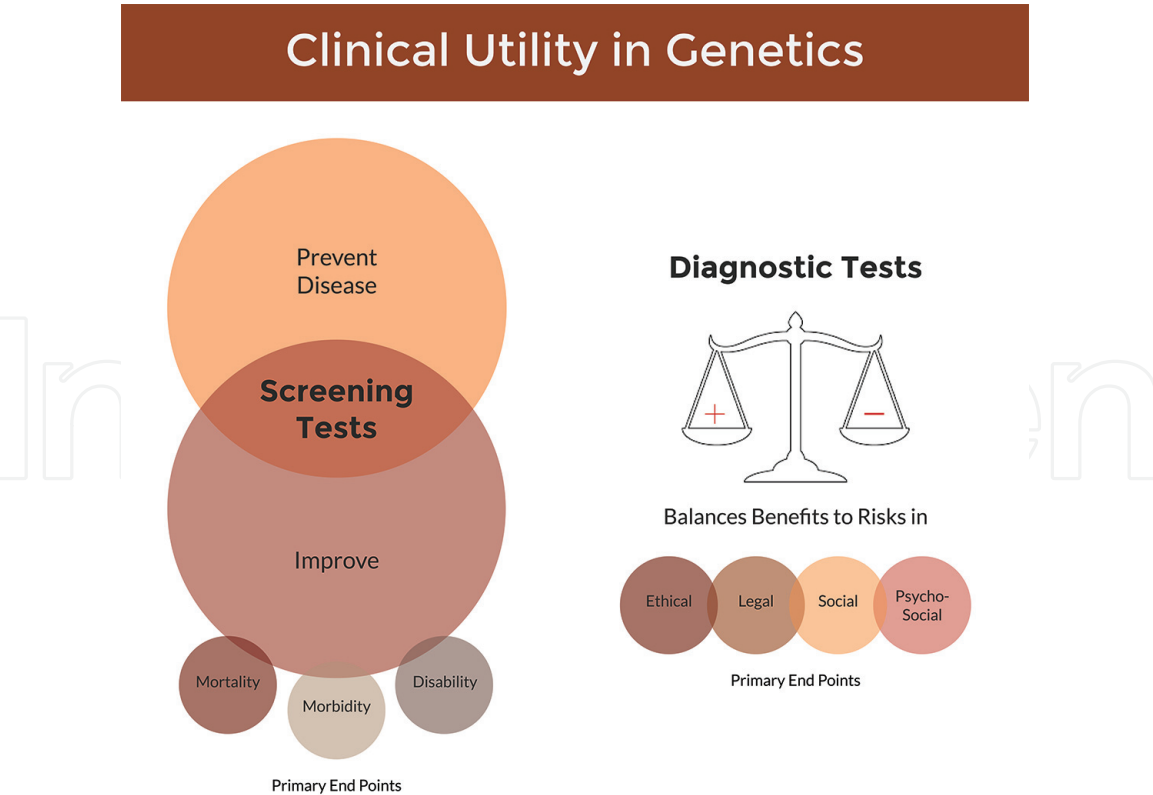
Figure 1.
Clinical utility in genetics. The clinical utility in screening tests is to provide preventative care and to improve primary end points such as overall morbidity; in a diagnostic setting, the value of genetic testing lies in the balance of benefits to risks in more psychological domains.

contextual or implementation issues (e.g., availability of resources) and that clinical utility can also include psychological benefits.

2.1 Evaluating genetic tests

Evaluating genetic tests is often methodologically difficult largely due to small patient populations and the resulting dearth of high-quality studies. Adapted from Morrison et al. 2012, the following subsections are generally agreed upon as common characteristics for reviewing genetic tests [3, 4].

2.1.1 Overview of disease and underlying genetics

- Information on the disease prevalence, treatments, and outcomes of the disease as well as overall cost

- Description of the genetic causes, including inheritance patterns

- Classifying the mutational spectrum, along with the prevalence and penetrance

- Determination if there is any "gold standard" tests to compare to

2.1.2 Target population and intended use

- Prevalence for target population involves age, ethnicity, and eligibility for testing

- Purpose of the test: is it diagnostic, for treatment, prognosis, management, carrier testing, prenatal testing, or other?

2.1.3 Laboratory information

- Validation details

  - Test new or already in use?

    - If already in use:

      - Number and rate of positive and negative mutations

      - Turn-around-time for results

      - Similar tests available

      - Current testing activity and expected with appropriate funding figures

      - Whether there are other laboratories that could offer the test

      - Infrastructure requirements

- Quality assurance, maintenance, and improvement programs—both internally and externally

2.1.4 Economic considerations

- Cost estimates for the test including equipment, personnel, and consumables/ reagents

- Costs of disease burden with or without treatment

- Costs saved by employing test

2.1.5 Analytic validity

- Precision, reliability, accuracy, sensitivity, and specificity of the genetic test, and how these compare with other employed screening and diagnostic tests

2.1.6 Clinical validity

- Specificity and sensitivity, positive predictive value, negative predictive value, likelihood ratios, and how these compare with other employed screening and diagnostic tests

2.1.7 Clinical utility

- Benefits and risks of the test

- Treatment of the patient

- Patient's health outcome

- Effect on patient and patient's family members

- Alternative diagnostic tests compare and contrast to genetic testing

2.1.8 Ethical, legal, and social

- Details on ethical, legal, and societal issues include support and follow-up

2.2 ACCE model and beyond

The CDC furthered the ACCE framework by establishing the Evaluation of Genomic Applications in Practice and Prevention (EGAPP) Initiative. The EGAPP supports the development and implementation of an evidence-based process for evaluating genetic tests and other genomic applications for clinical and public health practice. An independent, nonfederal EGAPP Working Group (EWG), consisting of a multidisciplinary expert panel selects topics of interest, reviews evidence, and recommends courses of action [2]. Key objectives of the EWG are to develop an openly accountable process, reduce conflicts of interest, and provide a connection between well-established evidence and the EWG recommendations [2, 5].

The ACCE model has stood the test of time and has proven to be a basis for the technical appraisal of genetic tests across the globe (**Figure 2**). The UK Genetic Testing Network and the Andalusian Agency for Health Technology Assessment expanded the ACCE model to guide the introduction of new genetic tests into their
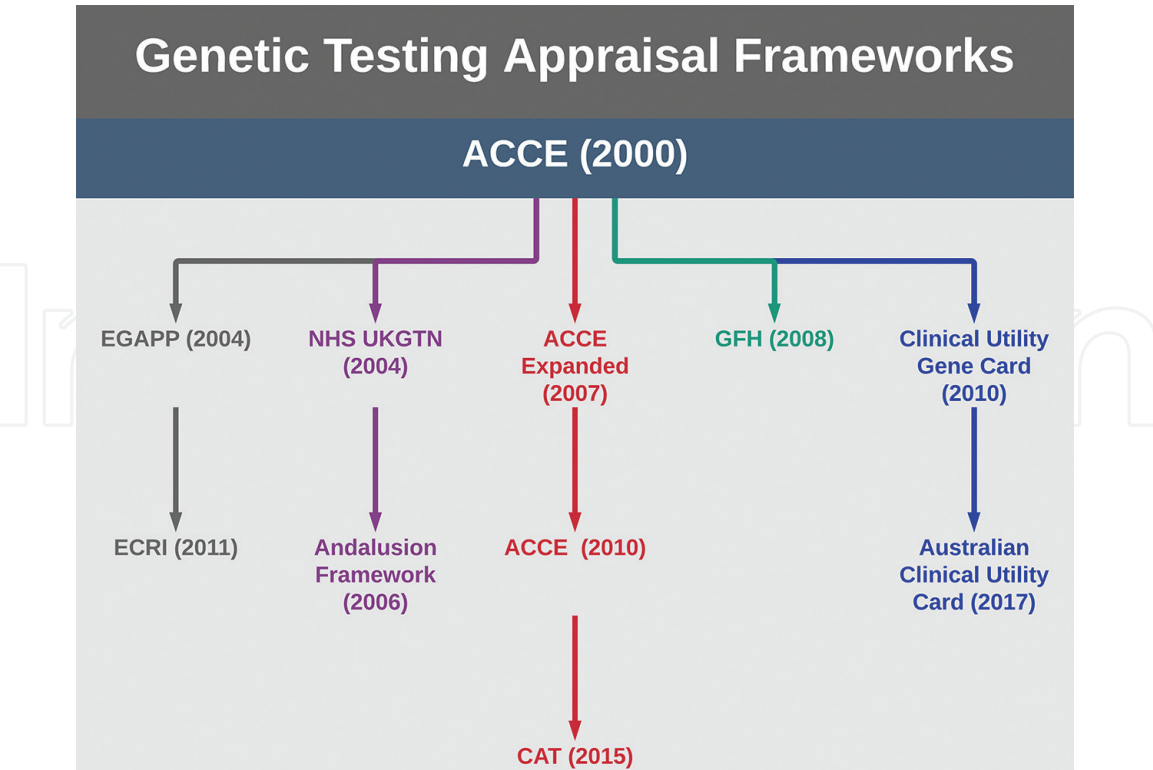

Figure 2.
Genetic testing appraisal frameworks. Testing appraisal frameworks around the globe have largely stemmed from the analytic validity, clinical validity, clinical utility, and ethical, legal and social implications (ACCE) framework announced in 2000. EGAPP, evaluation of genomic applications in practice and prevention; ECRI, Emergency Care Research Institute; NHS UKGTN, National Health Service UK Genetic Testing Network; CAT, companion test assessment; GFH, German Society of Human Genetics.

public health system, creating the 2004 NHS UKGTN Gene Dossier and the 2006 Andalusian Framework. In 2007, the ACCE model was again modified by adding health quality measures to the evaluation process. The process was made more streamlined, shortening the systematic review process for emerging genetic tests. In 2010, the ACCE model was adapted to particular types of genetic testing through the Complex Disease Framework and the ACHDNC Newborn Screening Framework of the Advisory Committee on Heritable Disorders in Newborns and Children. The ACCE model also spawned two European frameworks: the 2008 GFH Indication Criteria of the German Society of Human Genetics and the 2010 Clinical Utility Gene Card of EuroGentest. The 2015 Companion test Assessment Tool (CAT) build upon the ACCE model to determine which tests needed further evaluation. In 2011, the ECRI Institute utilized the EGAPP process to develop a set of analytical frameworks for various testing scenarios and other stakeholder aspects. Lastly, the EuroGentest inspired the 2017 Australian Clinical Utility Card [5].

We cannot ignore the influence of the stakeholders who will invariably have wildly different opinions as to which outcomes are considered relevant. Thus, the types of outcomes that must be considered in evaluating the utility of a genetic test will also depend on the purpose of the test and the congregation of those who make the final decision. For example, a state-funded public health program will likely focus on the overall impact on morbidity and mortality versus privately funded sectors concentrating on the greater net profit. Coverage decisions by third-party payers may be based in large part on perceptions that test results are useful for timely or accurate diagnoses and clinical management. For a test that is offered to families in a clinical setting on a voluntary basis, the value of information for making career, residential, and reproductive decisions take on greater relevance.

Before a genetic test can be accepted into clinical practice, data must be collected to demonstrate the benefits and risks that accumulate from both positive and negative results [1]. Referring back to the colorectal surgery example above, the term "clinical utility" fits in very well; however, when applied to genetics or genomics medicine, the term may be too limited. The clinical end points are extremely important, but the utility or actionable context must remain broad in genetics to embody an overall net benefit. Genetic testing is particularly useful in the psychosocial, ethical, legal, and social (ELS) realms as well as in many diagnostic cases (**Figure 1**). By including clinical and ELS together in the concept, improvements in health outcomes such as enhancements in morbidity, mortality, and in disability become strong primary end points when assessing the utility of genetic testing.

3. Genetic epidemiology: population and family-based studies

The process of genetic epidemiology has flowed sequentially from observing phenotypic differences between populations to demonstrating that diseases can run in families, to examining feasible genetic susceptibility models, to tracking co-segregating genetic markers with disease in families, to narrowing the region of candidate genes, to association analyses with candidate genes, to cloning and mutation identification, to functional and structural characterization of a gene, and, ultimately, to extending the phenotype characterization even further based on the genotype identified (**Figure 3**) [6].

Population and family-based studies are at the heart of genetic epidemiology. Population-based association studies are generally regarded as more statistically powerful than family-based studies, as they tend to have more subjects and are overall easier to execute [6]. Family-based designs are influential methods that use the proband as well as their relatives to assess the genetic and molecular
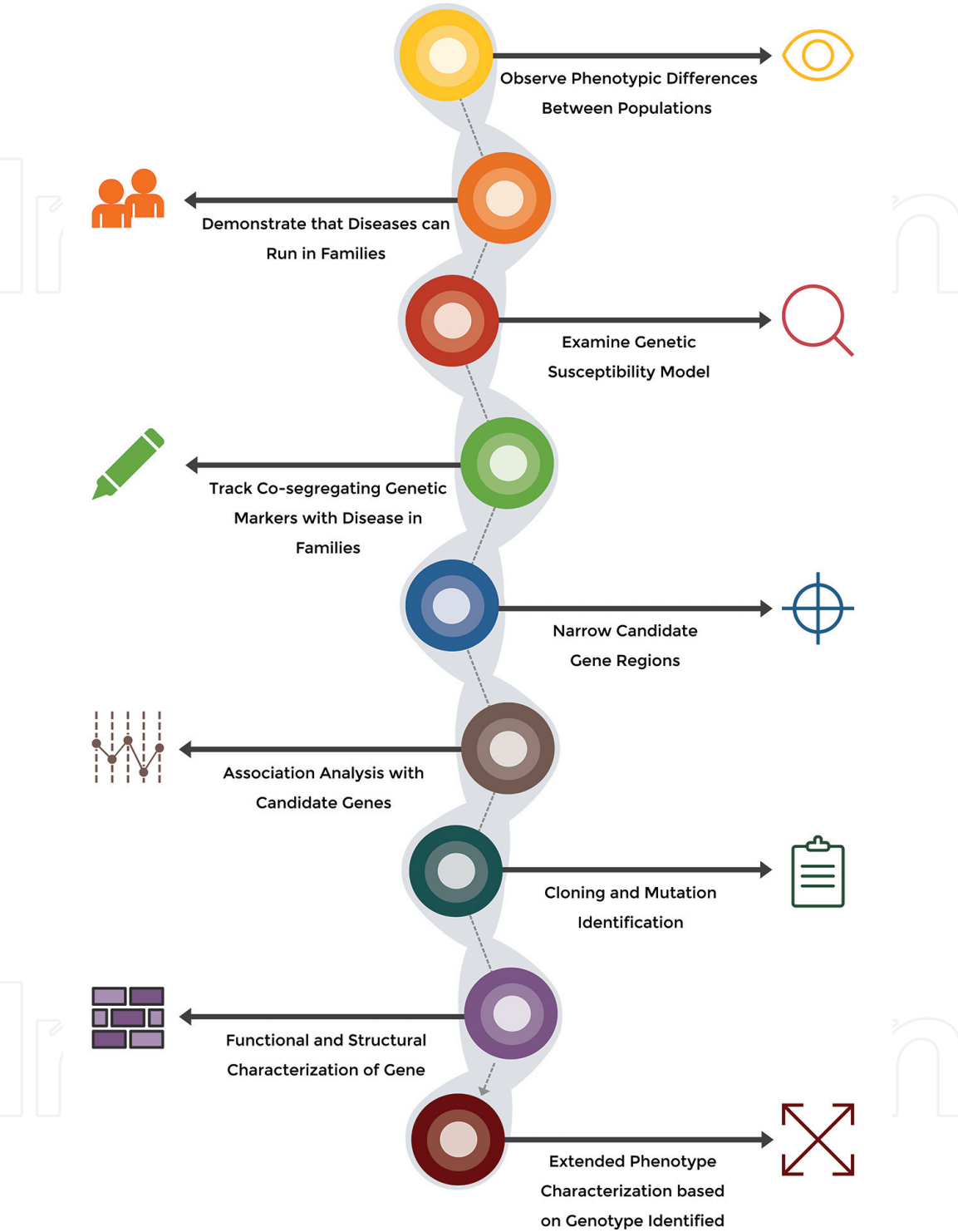
Genetic Epidemiological Historical Progression

Figure 3.
Genetic epidemiological historical progression.

epidemiology of disease (**Figure 4**). The various types of studies available include familial aggregation, twins, segregation, linkage, and association.

Linkage and association studies directly evaluate genetic markers and require the collection of DNA from the study subjects—as opposed to twin studies, segregation studies, and familial aggregations studies. Family-based studies have been the long-standing primary approach to detect disease-causing genes. Segregation and linkage studies are highly valuable methods for assisting in
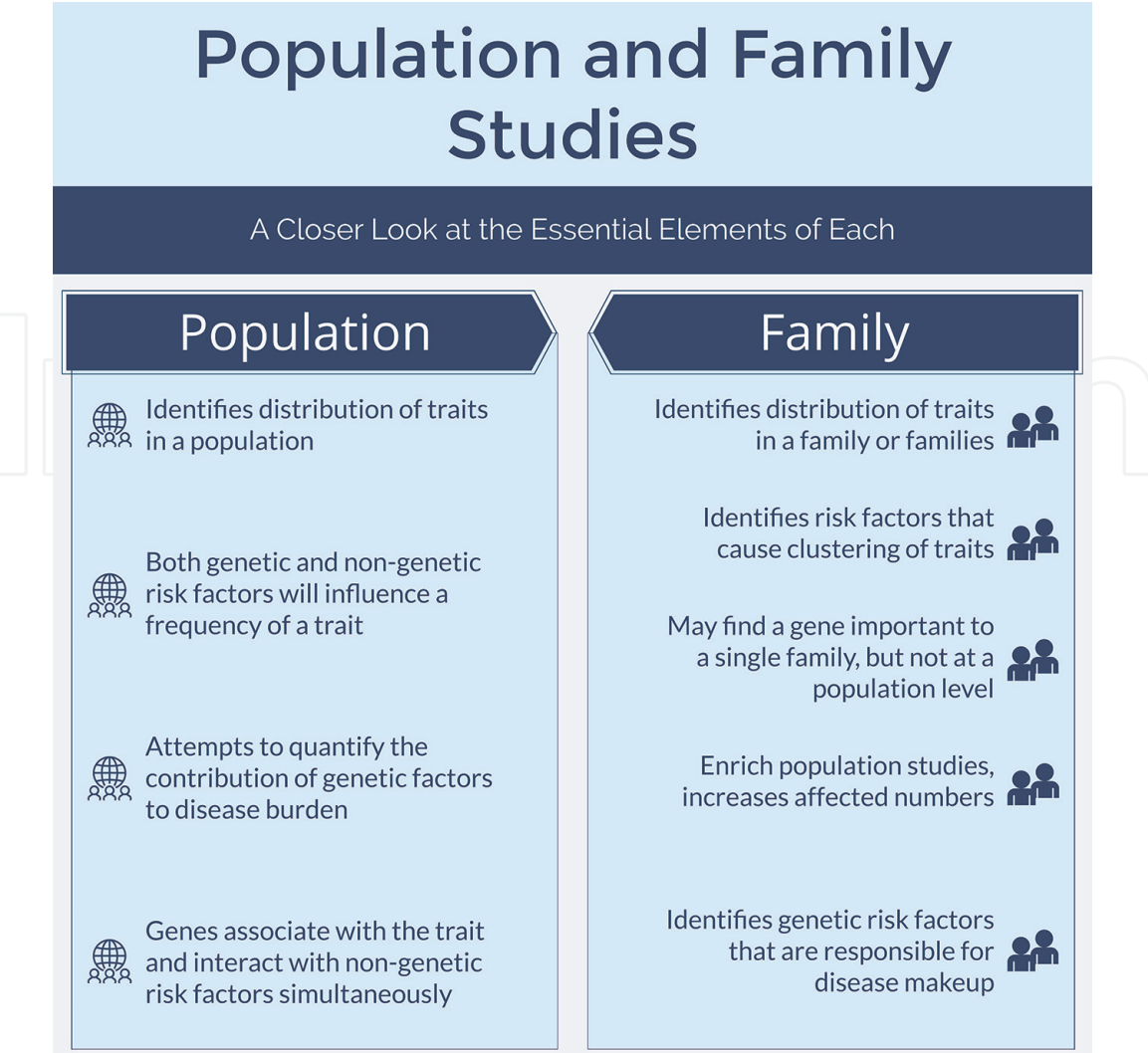
Population and Family Studies

A Closer Look at the Essential Elements of Each

Population

- Identifies distribution of traits in a population

- Both genetic and non-genetic risk factors will influence a frequency of a trait

- Attempts to quantify the contribution of genetic factors to disease burden

- Genes associate with the trait and interact with non-genetic risk factors simultaneously

Family

- Identifies distribution of traits in a family or families

- Identifies risk factors that cause clustering of traits

- May find a gene important to a single family, but not at a population level

- Enrich population studies, increases affected numbers

- Identifies genetic risk factors that are responsible for disease makeup

Figure 4.
A closer look at family-based and population studies.

cloning highly penetrant rare disease-causing genes. Family-based association studies strengths lie in their ability to control for confounding bias due to population stratification—albeit they do so at a loss of power [1, 5, 6].

Population stratification is when contrived associations can be detected if cases and controls come from different source populations that have systematic differences in ancestral allele frequencies. A great advantage of employing family-based study designs is that population stratification can be circumvented. By studying parents and their offspring/siblings, cases and controls within each family are virtually guaranteed to arise from the same sample source or population. Due to the increasing efficacy of identification of association with disease, the importance of family-based studies has seemingly subsided; however, it is worth pressing that family-based studies are arguably more important than they have ever been as they are still the only way to truly link a causative variant to disease [1, 5, 6].

Family-based studies can help determine whether a disease or trait is genetically influential by studying familial aggregation. Results can be furthered with a segregation analysis to identify the mode of inheritance. The results from the segregation analysis can add power to a linkage analysis, which searches across the entire genome in an attempt to locate regions containing causal genes [1, 5, 6].

Segregation analysis is a method of establishing the genetic inheritance of disease and is performed exclusively with family data. This approach assists in

determining if a disease segregates with a variant in a single gene; in addition to this, the mode of inheritance can also be ascertained. Very large pedigrees and families with a plethora of affected individuals are exceptionally informative for identifying specific genes [1, 5, 6].

Once a family is collected, and studied, in a segregation analysis, that family is generally made available for further analyses (e.g., linkage). Linkage occurs when two loci/alleles on the same chromosome are inherited together. Since recombination during meiosis can occur virtually anywhere in the genome it stands to reason that the closer two loci are to each other the less likely they will be separated after a recombining event (i.e., the more likely they are to stay together after recombination), that is, it says they are "linked." Linkage analyses utilize this phenomenon by investigating co-segregating genetic markers along with a disease trait seen within the family (or families)—the trait can be either qualitative or quantitative. If the markers and traits are observed to co-segregate within families, it can be logically inferred that the disease-causing variants are within close proximity to the markers [1, 5, 6].

This point reveals that linkage is "intrafamilial," whereby the co-segregating marker allele may very well be different in different families. Families are generally recruited into linkage studies on the basis of having at least one identified affected individual, and the families are either quite large or have affected siblings. Generally, the markers are spaced evenly over the entire genome, and linkage can be performed by utilizing these markers.

4. Breast and ovarian cancer: the journey of finding *BRCA1* and *BRCA2*

Establishing penetrance is an arduous undertaking even for some of the most well-studied genes (e.g., with *BRCA1* and *BRCA2*) simply because no two genetic studies have yielded the same findings. Many of the data and results discrepancies can be linked to differences in the populations studied and to the methodologies employed. It is vanishingly rare, if not impossible, for these studies to have similar methodologies to allow for perfect reproduction of results. The range of penetrance found for the BRCA variants and genes has guided the clinical recommendations for breast and ovarian cancer surveillance and prevention and has provided a sort of genetic "gold standard" by which all other genes are now compared and contrasted against [7, 8].

A strong family history of breast cancer is associated with an early age of onset, the addition of ovarian cancer, bilateral tumors, and a rarely affected male. *BRCA1* (and similarly for *BRCA2*) has been identified through the study of women who have presented with a strong family history of breast and ovarian cancer (**Figure 5**). In 1988, more than 1500 families with multiple cases of breast and ovarian cancer were studied; the data generated was subjected to a segregation analysis. The results illuminated that roughly 5% of cases, particularly those with early-onset disease, could be heritable in a Mendelian fashion. Selected families, those with near-Mendelian pedigree patterns, were aggregated for linkage analysis. A major susceptibility locus, *BRCA1* (OMIM 113705), was mapped to 17q21 in 1990. 17q-linked families that were above 45 years of age at diagnosis were given negative LOD scores.

In 1994, a linkage analysis performed on 15 large families with breast cancer that were also determined to not be linked to 17q helped identify the *BRCA2* locus located on 13q12 (OMIM 600185). Later that year *BRCA1* was cloned, and in 1995 *BRCA2* was cloned. *BRCA1* variants accounted for a very large proportion of
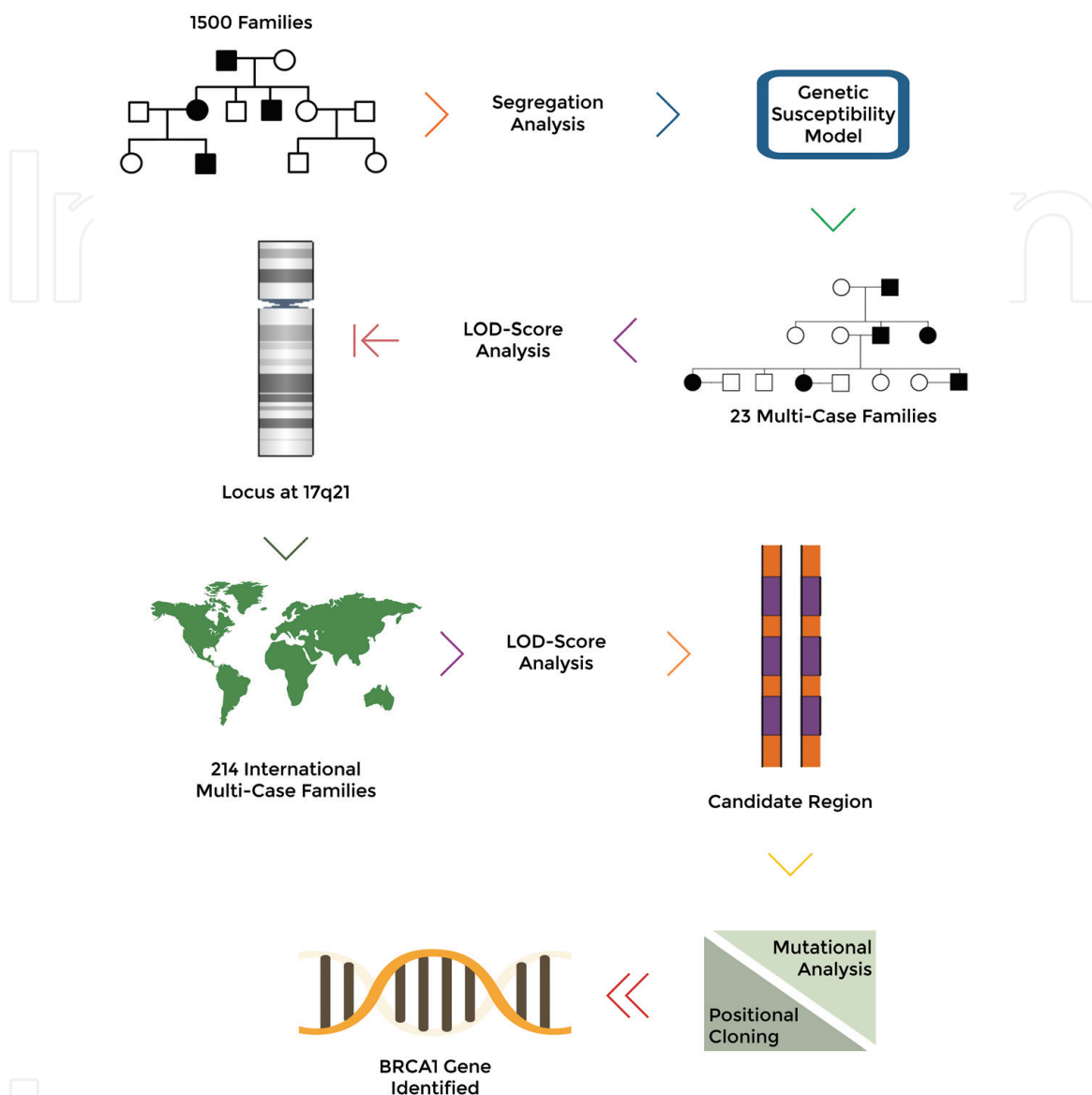
Figure 5.
The progression of discovering the BRCA1 gene.

families with both breast and ovarian cancers, while male breast cancer was predominately observed in *BRCA2* variant families [9].

BRCA1 and *BRCA2* were identified by focusing on a small number of specific families. Other candidate genes were established from focused studies.

- In 2004, the variant c.1100de1C in the *CHEK2* gene was observed in 201 cases (1.9%) and 64 controls (0.7%) in 10,860 breast cancer cases and 9065 controls from 10 case-control studies in 5 countries (estimated odds ratio (OR) 2.34; 95% CI 1.72–3.20; P = 0.0000001) [10].

- In 2006, the *ATM* gene was screened in individuals from specific families, and 12 mutations were found in affected individuals and in 2 controls (P = 0.0047) from 443 familial breast cancer pedigrees and 521 controls (estimated relative risk of 2.37 (95% CI 1.51–3.78, P = 0.0003) [11].

- *BRIP1* was initially described as a breast cancer predisposition gene in 2006. The analysis of 1212 women with familial breast cancer along with 2081 controls yielded mutations in 9 cases and in 2 controls (estimated relative risk of 2.0; 95% CI = 1.2–3.2; P = 0.012) [12].

- *PALB2* mutations were found in 10 cases of 923 individuals with familial breast cancer, and no mutations were found in 1084 controls (P = 0.0004) (estimated odd ratio of 2.3; 95% CI = 1.4–3.9; P = 0.0025) [13].

These factors are the most relevant in families where the disease and the variant are actually segregating together, but at a population level, their overall implication is surprisingly small. For instance, *CHEK2*:c.1100de1C, at a population level, is seen in only 1.9% of cases [14].

5. Less penetrant genes: *PALB2*, *BRIP1*, and *RECQL*

Traditionally, epidemiological studies tend to emphasize the inclination that the greatest benefits to the population are found in interventions that decrease risk factors for the bulk of the population, not in targeting a small number of individuals at the extreme ends of the risk spectrum. As we can see from the sample multigene panel for hereditary breast cancer the genes selected for testing range from quite influential (e.g., *BRCA1* and *BRCA2*) to marginally influential (e.g., *STK11*) (**Table 1**). However, it is quite interesting to explore the data for lower-risk genes such as *PALB2* and *BRIP1* and also for genes that are suspected of having involvement in breast or ovarian cancer, but the data is not quite yet congruent with the theory (e.g., *RECQL*).

Less penetrant genetic loci are mainly represented by the single-nucleotide polymorphisms (SNPs) or by the variants of uncertain significance discovered through genome-wide association studies. Variants associated with a minor increased risk, unlike high-risk mutations, can only account for a small portion of cancers seen in family histories of carriers. Thus, the cumulative risk for carriers with a positive family history will largely depend on the risk levels attributed to both their family history for that cancer and the risk induced by the variant itself. For example, if a carrier of a variant associated with an increased odds ratio of cancer also has a family history sufficient to quadruple her risk, her cumulative risk will be about that of a woman with a 4 x OR increased risk [7].

Mutations in *ATM*, *PALB2*, and *CHEK2*:c.1100delC, in conjunction with a strong family history, are very likely to be associated with a high absolute risk of breast cancer [17]. It is important to note that the family history creates a context whereby it changes the penetrance of these mutations. This interpretation is clinically important and would justify testing for these mutations in multi-case breast cancer families such as those seen by typical cancer family genetics services.

Genetic risk factors, which are familial by their very definition, will be more frequent in women with positive family histories involving multiple breast cancers through their direct association with breast cancer as a disease entity and with their direct association with the familial aspect of breast cancer. This can be illustrated in a simple example where we consider a rare mutation whose presence doubles the risk of breast cancer relative to the general population: it will be roughly four times more common in women who are affected and who have an affected first-degree relative, which will square the ratio [17].

Sample multigene hereditary breast cancer panel	
Gene	**Notes**
ATM c.7271 T > G	—
other *ATM* mutations	Lack of data regarding penetrance and surveillance except for c.7171 T > G mutation. If mutation has been identified, a careful assessment of residual risk for relatives who are noncarriers is needed
BARD1	—
BRCA1	—
BRCA2	—
BRIP1	—
CDH1	Increased risk of lobular breast cancer. Gastric cancer risk is unknown when mutations are identified in absence of a positive family history of gastric cancer
CHEK2 c.1100delC	Mutations are rare, but high penetrance in some families
other *CHEK2* mutations	Lack of penetrance data except for in specific mutations
NBN	—
NF1	Can identify mutation carriers by clinical phenotype and then perform gene specific test
PALB2	Mutations are rare, but high penetrance in some families
other *PALB2* mutations	—
PTEN	Can usually be identified by clinical phenotype
RAD50	—
STK11	Can usually be identified by clinical phenotype. Low penetrance in breast cancer
TP53	Breast cancer risk management inferred from other genes. High penetrance for breast cancer, but mutations are rare

Adapted from: Invitae and eviQ [15, 16].

Table 1.
Sample multigene panel offered for hereditary breast cancer.

5.1 PALB2

The Finnish founder mutation was found in 0.9% (18 of 1918) of cases without selecting for or emphasizing family history. Likewise, a French-Canadian founder mutation was found in 0.6% (2 of 356) of cases also without selecting for or emphasizing family history selected. The numbers of the *PALB2* founder mutation carriers were too small to make precise risk inferences, but modified segregation analyses of data from the families of case-carriers were used to estimate risk for carrier families, which has demonstrated the importance of these founder mutations in the risk of developing breast cancer [13, 14, 18, 19].

Blanco et al. found that the frequency of *PALB2* mutations was ~1.5% after investigating the incidence of mutations in *PALB2* patients with breast cancer that were also negative for any variants in *BRCA1* and *BRCA2* +/− a family history of pancreatic cancer; previous studies had the mutation rate for similar cohorts range from 0 to 4.8%. Dansonka-Mieszkowska et al. conducted similar research among Polish women; their study showed a minor but significant *PALB2* mutation presence at ~0.6% [13, 14, 18, 19].

Likewise, Bogdanov et al. conducted a study on the occurrence of *PALB2* mutations among Russian and German women and reported a mutation rate of ∼2%. In 2014, Antoniou et al. tested 362 women from 154 families and found that the risk of breast cancer in women 40 years of age or younger with *PALB2* mutation was ∼9x greater, ∼8x greater in patients aged 40–60 years, and ∼5x greater in patients 60 years and older when compared to the general population. The absolute risk of breast cancer in women with *PALB2* mutations under 70 years of age ranges from 33 to 58% for women without and with a positive family history of breast cancer, respectively. Interestingly, Hartley et al. conducted a study that confirmed that as the number of cases of breast cancer in a family increases, the likelihood of *PALB2* mutations increases as well. Women with 3+ positive cases of familial breast cancer have a 2.6% greater likelihood of having a *PALB2* mutation than those without multiple cases [13, 14, 18, 19].

Southley et al. studied Australian women to determine the occurrence rate and penetrance of *PALB2* mutations. The study found that the women with breast cancer and a positive family history of having *PALB2* mutations had *PALB2* mutations present in 1% of patients. The study identified that the women with breast cancer and no family history of *PALB2* mutations had *PALB2* mutations present in only ∼0.4% of patients. There were no *PALB2* mutations detected in the control/healthy population of women. Heikkinen et al. studied southern Finnish women and found *PALB2* mutations in 2% of patients with a positive familial history of breast cancer and also in 0.6% of women with a sporadic breast cancer presentation [13, 14, 18, 19].

In 2016, a seminal paper by Thompson et al. examined 2000 predominantly breast cancer-affected women with a strong family history that were also *BRCA1* and *BRCA2* variant-negative and compared them to 1997 controls. They observed that a significant proportion of mutations were only in *PALB2* (26 cases vs. 4 controls) and in TP53 (5 cases vs. none in controls), whereas no mutations were identified in *STK11* [14]. *PALB2* is a great example of how penetrance estimates can depend on the population, family history, and age at onset as well as other considerations [17].

5.2 BRIP1

BRIP1 was initially described as a breast cancer predisposition gene in 2006. The analysis of 1212 women with familial breast cancer along with 2081 controls yielded mutations in 9 cases and in 2 controls (estimated relative risk of 2.0; 95% CI = 1.2–3.2; P = 0.012). However, recently *BRIP1*'s association with breast cancer has grown suspect, while its association with ovarian cancer has risen sharply. *BRIP1* mutations confer a high ovarian risk in familial index patients (OR = 20.97, 95% CI = 12.02–36.57; P < 0.0001) and in the subgroup of patients with late onset ovarian cancer (OR = 29.91, 95% CI = 14.99–59.66; P < 0.0001) [12].

5.3 RECQL

In a screen of 144 Polish and 51 French-Canadian women with early-onset familial breast cancer, 2.6% possessed truncating mutations in *RECQL*. Validation studies that reviewed the *RECQL* variant c.1667_1667C3delAGTA in over 13,000 breast cancer patients with 4702 Polish controls showed the *RECQL* mutation appeared in 0.23% of cases and in 0.04% in controls. Likewise, the *RECQL* variant c.634C > T (p. Arg215*) seen in the French-Canadian population was further screened in 538 patients and 7136 newborn controls and was detected in 5 patients and in one control—a nearly 50x increase in frequency in affected versus

unaffected individuals. Studies of patients in northern China revealed a pathogenic *RECQL* mutation in 2.0% of the 448 familial breast cancer patients compared to the 0.06% seen in 1588 control subjects [20]. By whole exome sequencing 0 early-onset familial breast cancer patients without *BRCA1*/2 mutations and by screening the *RECQL* gene in an additional 439 unrelated familial breast cancer patients, 9 index cases were found to carry a pathogenic mutation in the *RECQL* gene among the 448 BRCA-negative familial breast cancer patients. It was determined that the pathogenic mutation rate of the *RECQL* gene in familial breast cancer in *BRCA1-/BRCA2*-negative breast cancer patients was 2.0%. Further to these results, no loss of heterozygosity was found in the *RECQL* mutation carriers, suggesting that *RECQL*-associated tumorigenesis is likely through classical haploinsufficiency [21].

In 2018, Li et al. sequenced all the exons of RECQL and at least 10 bp of the exon–intron flanking regions in 9112 subjects from Australia. The case subjects were females diagnosed with breast or ovarian cancer from 4536 families with a negative result after BRCA1 and BRCA2 mutation testing. The controls were 4576 women who were above 40 years of age and were cancer-free as of May 2016. Thirteen loss-of-function mutations in the cases and 25 in the controls were identified (0.29 versus 0.55%, odds ratio 0.52, 95% confidence interval 0.25–1.06, $P = 0.072$ by two-tailed Fisher's exact test) [22]. Missense variants observed between cases and controls were not statistically significant (54 cases, 1.19%, versus 37 controls, 0.81%; $P = 0.073$) [22]. It is generally accepted that a predisposition gene is considered actionable only if the 90% confidence limit of the estimated relative risk is greater than four [22]; therefore, RECQL, can be excluded based on these findings.

5.4 Lack of data and the impact of finding a variant of unknown significance

Despite the intense and widespread shared enthusiasm to reduce the risk of predictable cancers, the adoption of the more recent breast cancer predisposition genes, such as *PALB2*, has been sluggish. This has been largely due to the communal appreciation that following a variant of unknown significance result, the complexity of interpretation may lead to a subsequent clinical utility hindrance. An additional 3.9% of patients tested by multiple gene panels had pathogenic mutations identified in other breast cancer predisposition genes, namely, in *PALB2*, *CHEK2*, and *ATM*; however, many of these multigene panel tests also identified many variants of uncertain significance, where the classification is either uncertain or simply just not possible—and this information cannot safely be utilized clinically [19].

Indeed, this consideration is shared in recent literature and has been extended by Thompson et al. where the authors examined various genes that are common on hereditary breast cancer panels. They observed that the frequency of mutations in most breast cancer panel genes is quite low, or even, in most cases, similar to the frequency of mutations observed in cancer-free population controls. They concluded that panels have the potential to provide clinical misinformation and harm at the individual level if the data is not interpreted with extreme caution [14]. This lack of evidence for new genetic players is not limited to breast and ovarian cancer, but it also plagues many other genetic diseases and also afflicts a great number of other multigene panels [19].

Due to this lack of supportive data, international large-scale studies into the genes included in these multigene panels are absolutely critical to increase the utility of the information yielded and also to ensure that the new genetic information presented is both safe and useful in a clinical setting.

6. Conclusions

Keeping in-line with global regulation entities such as CAT, EGAPP, NHS UKGTN, and the ACCE backbone discussed above, the recent initiative eviQ provides a variety of guidelines for cancer genetics investigations. EviQ is part of the Cancer Institute NSW (New South Wales) and provides evidence-based information to support health professionals in the delivery of cancer treatments available at the time treatment decisions are being made. We can see from the eviQ's general practitioner referral guidelines for cancer genetics assessment that generally, even in oncology, genetics plays a large part in the diagnostics of disease [23]. We can also note that there must be a strong clinical suspicion of the diagnosis involving a genetic element (e.g., quite young, strong family history, hailing from a region with restricted gene flow, etc.) to warrant testing and for it to be useful.

The clinical utility of genetics is highly variable and dependent on the gene or disorder involved, but genomics medicine appears to be very good at revealing a diagnosis, and, at times, it can help explain why the phenotype is the way it is. In oncology, genetic testing plays an integral role in disease management by influencing treatment options or by being a major inclusion component for clinical trials. Where genetic testing is taking off and, perhaps, where its true potential lies is in its ability to offer predictive and preventative medicine, particularly for families, as opposed to adhering to a purely reactive approach that is typically employed in mainstream medicine.

Genomics is by no means irrelevant; it is revealing much about human disease and pathophysiology, but barring the current leaps and bounds observed in oncology, genomics medicine is still in an informational gathering phase—albeit, it is doing so at an alarming and unparalleled rate. It will take a great deal more data, analysis, and time before it will be considered true mainstream medicine, but there is no doubt that genomics is the future of medicine.

Conflict of interest

The authors declare no conflict of interest.

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