TRANSLATIONAL GENOMICS: THE IMPACT OF GENETIC RISK SCORE ON PATIENTS AND PHYSICIANS

BY

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DEDICATION AND ACKNOWLEDGMENTS

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ABSTRACT

Genomewide Association Studies have identified thousands of associations between genetic markers and complex disease risk. When several of these markers are used in combination, the predictive performance is strong; however, the clinical utility of multi-marker tests is not known. This thesis addresses a unifying question: Can genomic test results safely and effectively target healthcare decisions for patients and physicians?

For patients, we conducted a randomized trial of multi-marker genomic test risk assessment versus family history risk assessment, giving risk results to 700 study participants. During three years of follow-up, we found no evidence that multi-marker genomic testing increases anxiety or subsequent uptake of prostate cancer screening. Level of risk was associated with subsequent cancer screening in the group that received multi-marker risk results, but not the group receiving standard family history risk assessment. This is likely the first randomized trial to find that multi-marker genomic risk results can motivate targeted uptake of cancer screenings by those at highest risk. This is important because the ability to target cancer screening to those at highest risk has been suggested as an important approach for reducing side effects and financial costs.

For physicians, we evaluated the readiness of Primary Care Providers to utilize multi-marker genetic tests in the clinic. We tested whether short educational sessions address known barriers to clinical use of genetics, including limited knowledge, costs, time, and discrimination. The session significantly increased confidence explaining genetic test results to patients, as well as many educational, logistical, and ethical aspects of genetic
testing. This is one of the first studies to show that short educational sessions on emerging technologies effectively build upon existing genetics knowledge, efficiently preparing them to utilize new genomic testing technologies.

Together, these projects suggest a path forward for translation of genomic technologies from the laboratory to the clinic.
CHAPTER I
INTRODUCTION

This introductory chapter is partially based on two publications:


When the first successful Genome-Wide Association Study (GWAS) was published in 2005, it not only revealed genetic variants associated with age-related macular degeneration, but it also showed that the GWAS approach could be successful [1]. This ushered in a rush of additional GWAS studies. GWAS provided researchers with a new tool to identify genetic associations with a variety of phenotypes, and was especially powerful for evaluating common phenotypes.

Almost as rapidly as GWAS studies were providing new discoveries, a debate emerged regarding clinical applications of the findings. Several companies pushed forward with commercial offerings of direct-to-consumer testing for multiple GWAS variants. Some clinicians began to consider how to implement new multi-marker GWAS testing, and the
term “personalized medicine” took hold. Others, often those speaking from a public health perspective or a medical genetics perspective, pointed out the unknown impact of this new genetic information on patients and unknown readiness of healthcare providers.

The current thesis considers the opportunities and concerns of personalized medicine. Specifically, we focused on the clinical application of multi-marker genomic tests for prostate cancer that are based on the findings from GWAS. Accordingly, the translational research described herein was based on two Specific Aims within a larger project:

Aim 1. To compare the provision Family History (FH) versus Genetic Risk Score (GRS) for Prostate Cancer (PCa) risk from the perspective of at-risk patients.

Aim 2. To evaluate whether a short educational intervention can address key barriers to clinical implementation of GRS among primary care providers.

The remainder of this introductory chapter provides the framework through which we addressed these Aims, by reviewing key topics; Prostate Cancer and Screening, Germline genetics of PCa, GWAS for Prostate Cancer, Potential multi-marker application of GWAS findings, Personalized Medicine for PCa, Debate on clinical applications, Questions of health benefit, Translational research, and Hypothesis and approach. Chapter II addresses Aim 1, and Chapter III addresses Aim 2.
Prostate Cancer and Screening

PCa is the most common cancer in US men and the second leading cause of cancer-related death, with about 181 thousand new diagnoses and 26 thousand deaths estimated to occur in 2016 [2]. These statistics translate to average lifetime risks of 1 in 7 men being diagnosed with PCa and 1 in 39 men dying from PCa [2]. PCa mortality significantly decreased following widespread introduction of Prostate-Specific Antigen (PSA) screening in the 1990s; however, it was not clear whether PCa screening versus advances in treatment were responsible for the observed reduction in mortality [3,4].

PSA screening brings downstream risks, leading about 1 million U.S. men to have a prostate biopsy each year; about 70% to 75% of these men are found to not have PCa [5]. Of the approximately 250 thousand men found to have pathology-defined PCa, many are subjected to treatments that include surgery, radiation, hormone blockers, and chemotherapy, all of which impact quality of life. As outlined in the next paragraph, to save one life, thousands of men would need to be screened and dozens of the resulting cases would need to be subjected to unnecessary treatments and the resulting side effects. This is the crux of the arguments against PSA screening for PCa.

Two large prospective studies attempted to resolve the PSA screening controversy [3-8]. Starting in 1993, the Prostate, Lung, Colorectal, and Ovarian (PLCO) Screening Study [6,7] followed nearly 77 thousand men for 10 years and found no reduction in mortality between the “PSA screening arm” versus the “non-PSA screening arm”; however, critics noted high levels of contamination (i.e. PSA screening) among participants in the control
(i.e. non-screening) group, thus indicating the study did not actually compare the impact of PSA screening versus non-screening on mortality, and thus might not have had sufficient power to detect significant differences [3,4]. In contrast, a significant 20% reduction in PCa mortality was reported by the European Randomized Study of Screening for Prostate Cancer (ERSPC) [3,8], which has randomized and followed more than 162 thousand participants to PSA screening or non-PSA screening arms. Additional analysis for 12 years of follow-up found a 31% reduction of metastatic PCa. While the reduction in mortality observed in ERSPC justified the ability of PSA to save lives, the question of “what cost?” remained; overdiagnosis of indolent PCa remained a key concern because to prevent one death from prostate cancer, 48 cases of prostate cancer would need to be treated, and 1410 men would need to be screened [8]. That is, most PCa identified by PCa is indolent and will not lead to death, while treatment may have a significant impact on quality of life. In 2010, as a result of those findings from large randomized trials, the U.S. Preventive Services Task Force (USPSTF) recommended against routine screening, citing over-diagnosis and over-treatment leading to unnecessary risks [9]. In contrast, the American Cancer Society (ACS), American Urological Association (AUA), and European Association of Urology (EAU) maintain PSA screening should be considered, but only after physician-patient discussion of the risks and benefits [10-12]. Commentaries on those prospective trials and the resulting recommendations have made the case that a favorable balance of risks and benefits can be achieved by targeting PSA screening to patients that can gain the most, while reducing screening among those who will gain little [3,4,13].
Germline genetics of PCa

A variety of risk factors have been proposed as underlying PCa risk and mortality; however, the only confirmed risk factors to date are age, race, and family history. It is arguable that genetic inheritance plays a significant role in the pathogenesis of PCa, as demonstrated by the observation that the risk of PCa increases with additional affected first degree relatives [14], and by the findings from a large twin study determining that the heritability of PCa is 42%, being notable as the greatest among all common cancers [15]. These findings highlighted the need to identify, and study the role of, inherited (germline) genetic variants in association with altered risks for PCa onset or progression. Initially, linkage studies and candidate gene association studies were the primary tools used in this search.

From about 1995 through 2005 genome-wide linkage studies and candidate gene-based association studies were the primary tools used in the search for germline genetic variants for cancer, including prostate cancer [16-24]. Genome wide linkage studies were used to identify chromosomal regions harboring susceptibility genes in hereditary prostate cancer (HPC) families, typically defined as three or more first degree affected relatives. Linkage results have led to the identification of several loci potentially involved in HPC, including $HPC1$ [22] $RNASEL$ [23], and $MSRI$ [24]. However, these are not major risk genes on par with $BRCA1$ and $BRCA2$ for hereditary breast cancer or $MSH2$ and $MLH1$ for hereditary nonpolyposis colorectal cancer (HNPCC). Candidate genetic association studies were conducted using case-control designs to examine variants in candidate genes and later in candidate pathways. For the most part, candidate genes-based association
studies failed to consistently demonstrate that specific genetic variants were associated with PCa risk or prognosis; results that were initially promising were largely not confirmed by subsequent independent studies, and those that were confirmed appear to confer very modest alteration of PCa risk [25,26]. Overall, findings from candidate gene association studies and linkage studies remain unlikely to lead to clinical applications.

**Genome-wide association studies for PCa.**

GWAS seeking to identify risk factors for a particular disease phenotype will typically begin with a case-control study, although case-case designs are used when the aim is to identify associations with disease severity. A carefully defined phenotype is critical to GWAS. Cells, typically blood or buccal in origin, are collected from thousands of study subjects for subsequent Deoxyribonucleic acid (DNA) extraction. This DNA can then be used for microarray-based genotyping of millions of Single Nucleotide Polymorphisms (SNPs). GWAS data must undergo a systematic quality control process, with adjustment for population stratification. Then tests of association are performed between SNPs and disease phenotypes, allowing for comprehensive and unbiased assessment across the genome. This basic study design has been adapted to many specific applications, and allowed for the identification of novel associations of SNPs with many complex diseases including cancer.

As evidence of the diverse utilization of GWAS, the online reference, “The NHGRI-EBI Catalog of published genome-wide association studies” lists approximately 1772 SNPs associated with 174 cancer phenotypes as of March 7, 2016 [27,28]. For PCa, 294 SNPs
met the minimum threshold for inclusion in the GWAS catalogue \( (p < 1.0 \times 10^{-5}) \), and 76 SNPs met a more significant threshold \( (p < 1.0 \times 10^{-8}) \), as of March 20, 2016 (Figure I-1).

The catalogue also includes two GWAS SNPs that are associated with aggressive PCa [28]. Beyond cancer, the catalog includes associations with many additional common diseases such as diabetes, asthma, cardiovascular disease. Associations listed in the catalog meet stringent criteria for genome-wide statistical significance and have been validated in independent study populations, all but eliminating the likelihood of chance associations.

**Figure I-1.**

Diagram of 76 SNPs associated with Prostate Cancer at Genome-Wide Significance \( (p < 1.0 \times 10^{-8}) \), mapped to each chromosome, as of March 20, 2016.

The question is, what did GWAS ultimately yield? Unlike most single-gene association studies that preceded the new GWAS approach, association results from GWAS were confirmed in multiple independent study populations, strongly suggesting the
associations are not false positives, but rather are true markers of the associated phenotype. Unlike prior linkage studies that had located wide genetic regions that were probably most relevant to rare hereditary phenotypes, GWAS implicated relatively small regions (haplotype blocks) containing genetic variants associated with common phenotypes that affect the majority of most any population. Importantly, most of the risk alleles of SNPs identified by GWAS are common (>5%) in the general population, meaning they might have potential utility in the general population, another key contrast to the rare variants known from prior Mendelian genetic studies. From a functional standpoint, GWAS identified many phenotype associations with the risk alleles of SNPs that are located in introns or intergenic regions (i.e. “gene-deserts”) of the genome, suggesting traditional molecular mechanisms that were known from Mendelian genetics might not apply. Most of the independent SNP associations have a small effect on disease risk, with 1.2 Odds Ratios (ORs) on average, raising significant doubt for their clinical utility. [29,30]

**Potential multi-marker application of GWAS findings**

Despite the small individual effect of each SNP on disease risk, an important paradigm shift occurred when it was discovered that multiple SNPs could be combined into a panel, and the risk alleles assayed, allowing for significantly larger ORs to be observed for prostate cancer (PCa) and breast cancer [31-34], as well as many other common diseases. For example, when the first five PCa risk-associated SNPs identified from GWAS and family history were examined, men who have five or more of these risk factors have OR of 9.46 for PCa, as compared with men without any of the risk factors [31]. Absolute risk
can be calculated for individuals based on the SNP-specific Relative Risk (RR), calibrated incidence rate of PCa, and mortality rate for all causes excluding PCa in the U.S [32,35]. In a population based study of 2,893 PCa cases and 1,781 controls, Xu et al found that, among individuals with a positive family history, the lifetime risk of PCa jumps from 23% to 52% among those who carry the population average number of risk alleles (n=11 risk alleles, average) versus individuals carrying 14 or more risk alleles [32]. A similar increase was also observed among men with a negative family history; from an 11% lifetime risk (n=11 risk alleles, average) to a 24% lifetime risk (n≥14 or more risk alleles) [32]. These trends are shown in Figure I-2.
To put this into perspective, the cumulative levels of PCa risk as predicted by associated risk alleles of SNPs are comparable to current population risk screening methods for various other types of cancers, such as for lung cancer based on smoking status [36], or breast cancer based on mammography [37]. The germ-line genetic markers discovered by GWAS are unique in that they can be objectively and accurately measured, do not change with age, and always precede associated phenotypes. Discovery of these
increased risks provided the first hint that SNPs discovered by GWAS had real potential for clinical application in risk prediction, that is, personalized medicine.

**Personalized Medicine for PCa**

As more GWAS results were published, and as we came to fully appreciate the ability to combine multiple risk SNPs into a testing panel, the idea of Personalized Medicine crystallized. The aim of Personalized Medicine is to provide individual risk assessment for medical conditions or to predict the efficacy of measures intended to monitor, prevent, or treat these conditions [38]. Personalized Medicine could be important in addressing the clinical and public health issues involved in a variety of diseases, including cancers that are detected via population-level screening. This could be particularly relevant to PCa, where concerns have been raised regarding prostate-specific antigen (PSA) screening, subsequent over-diagnosis of low-grade diseases, and ultimately over-treatment of many indolent cancers that for the most part are not life-threatening. Improved risk estimation may help to address this major public health problem, as the prostate is the most common site of cancer diagnosis, accounting for approximately 30% of all new cancer diagnoses, and 11% of cancer deaths, in US men. This translates to an estimated 220,900 prostate cancer diagnoses and 28,900 deaths, in U.S. men each year [2].

**Debate on clinical applications**

Despite the strong statistical evidence and the promise of personalized medicine, there are ethical and technical arguments for and against clinical applications of these SNPs.
discovered by GWAS. Many of the arguments deal with the clinical validity and clinical utility of the associated SNPs [39,40].

Ethical concerns center on the balance of benefit versus risk (beneficence/non-maleficence). Thus if high-risk results create excessive anxiety, or if low-risk results create a false sense of security, either of these may lead to inaction or over-reaction in subsequent medical decisions, such as whether or not to have PSA screening in men or mammography in women. On the other side of the argument, autonomy could be emphasized while condemning paternalism, giving individuals the right to make informed decisions to access their own personal genetic information. The argument is, patient or physician knowledge of this genetic information is not inherently dangerous, and perhaps patients could obtain some benefit from this new technology if we begin to examine how to appropriately implement these new genetic markers in clinical settings. Some may remain concerned about increased potential for genetic discrimination as genetic testing goes more mainstream, while others counter that legal protections such as the Genetic Information Non-discrimination Act of 2008 (GINA) are already in place.

Various technical concerns have been raised as well. First, many of these associated SNPs are located in non-coding and intronic areas of the genome, and the molecular mechanisms by which they act is poorly understood, thus leaving their causal role in question. While most GWAS associations cannot be explained based on our existing knowledge of causal mechanisms, GWAS findings have provided many novel biological insights that serve as leads for additional studies. For example, a Chromatin Immunoprecipitation on DNA microarray (ChIP-on-chip) study has suggested an
interaction between androgen receptor binding sites and many of the prostate cancer associated SNPs, suggesting an androgen dependent pathway by which many of these SNPs act [41]. Study designs such as these together with a more comprehensive assessment of the genome and a better understanding of the role of non-coding regions will result in an appreciation of the functional significance of these SNPs. Next-generation sequencing, epigenetic studies, and proteomics could help reveal the functional impact of these sets of variants, which will be important to understand etiology and to eventually develop targeted therapies. However, considering the huge number of associated variants, the process of functional characterization and therapeutic development may require years, or even decades, to complete. It is difficult to imagine that laboratories will ever complete the job of characterizing the functional impact of every genetic variant. Therefore, functional characterization should probably focus on the variants that have the greatest impact on risk or the greatest potential for therapeutic intervention. Complete functional characterization of the genome should not be an impediment to other lines of applied research, and there is nothing wrong with doing the best we can with what we have available at a given point in time. Given the massive public health impact of common diseases such as cancer, it could be argued that we should move forward with utilizing the best currently available information; indeed, that is exactly the model that was used for BRCA1/2 testing, where clinical testing was offered in medical genetics clinics well before we had any clarity regarding the mechanistic underpinnings. Although all of the biological mechanisms are not yet understood, we already know that GWAS findings represent true associations in populations, based on consistent observations across independent study populations. This
supports the need for additional research to evaluate the validity and utility of these SNPs for risk prediction. Risk-assessment testing does not preclude additional mechanistic research into the causal role of current SNPs or the discovery of additional variants; rather results from GWAS should continue to stimulate additional research in closely related fields.

Another persistent technical concern is based on the fact that the predictive performance of GWAS markers is generally modest as estimated by the area under the curve (AUC) statistic of the receiver operating characteristic (ROC) [42-44]. In the case of PCa, an AUC of 62% can be obtained when using the very best baseline clinical parameters in combination (age, family history, free/total PSA ratio, number of cores at pre-study entry biopsy, and prostate volume) to predict PCa among repeat biopsies in the REDUCE study, which is 12% higher than chance (50%) [45]. When 33 PCa risk-associated SNPs (Table I-1.) are added to these clinical parameters, an AUC of 66% is observed, and this increase in AUC is statistically significant [45]. Although this AUC only represents a 4% absolute increase, it represents a 33% (4%/12%) relative improvement over the best clinical risk prediction model [45]. As additional risk variants are identified and validated from GWAS and other methods, the AUC of the prediction model should continue to increase.
Table I-1.
Summary of SNPs reproducibly associated with PCa as of 2011, assayed in the REDUCE study described above and in the new study described in chapter II.

<table>
<thead>
<tr>
<th>CHR</th>
<th>SNPs</th>
<th>Region</th>
<th>Position</th>
<th>Known genes</th>
<th>m/M allele</th>
<th>Risk allele</th>
</tr>
</thead>
<tbody>
<tr>
<td>2</td>
<td>rs1465618</td>
<td>2p21</td>
<td>43,407,453</td>
<td>THADA</td>
<td>A/G</td>
<td>A</td>
</tr>
<tr>
<td>2</td>
<td>rs721048</td>
<td>2p15</td>
<td>62,985,235</td>
<td>EHB1</td>
<td>A/G</td>
<td>A</td>
</tr>
<tr>
<td>2</td>
<td>rs12621278</td>
<td>2q31.1</td>
<td>173,019,799</td>
<td>ITGA6</td>
<td>G/A</td>
<td>A</td>
</tr>
<tr>
<td>3</td>
<td>rs2660753</td>
<td>3p12</td>
<td>87,193,364</td>
<td>--</td>
<td>T/C</td>
<td>T</td>
</tr>
<tr>
<td>3</td>
<td>rs10934853</td>
<td>3q21.3</td>
<td>129,521,063</td>
<td>EEFSEC</td>
<td>A/C</td>
<td>A</td>
</tr>
<tr>
<td>4</td>
<td>rs17021918</td>
<td>4q22.3</td>
<td>95,781,900</td>
<td>PDLIM5</td>
<td>T/C</td>
<td>C</td>
</tr>
<tr>
<td>4</td>
<td>rs7679673</td>
<td>4q24</td>
<td>106,280,983</td>
<td>TET2</td>
<td>A/C</td>
<td>C</td>
</tr>
<tr>
<td>6</td>
<td>rs9364554</td>
<td>6q25</td>
<td>160,753,654</td>
<td>SLC22A3</td>
<td>T/C</td>
<td>T</td>
</tr>
<tr>
<td>7</td>
<td>rs10486567</td>
<td>7p15</td>
<td>27,943,088</td>
<td>JAZF1</td>
<td>A/G</td>
<td>G</td>
</tr>
<tr>
<td>7</td>
<td>rs6465657</td>
<td>7q21</td>
<td>97,654,263</td>
<td>LMTK2</td>
<td>T/C</td>
<td>C</td>
</tr>
<tr>
<td>8</td>
<td>rs2928679</td>
<td>8p21.2</td>
<td>23,494,920</td>
<td>SLC25A37</td>
<td>A/G</td>
<td>A</td>
</tr>
<tr>
<td>8</td>
<td>rs1512268</td>
<td>8p21.2</td>
<td>23,582,408</td>
<td>NKX3.1</td>
<td>T/C</td>
<td>T</td>
</tr>
<tr>
<td>8</td>
<td>rs10086908</td>
<td>8q24 (5)</td>
<td>128,081,119</td>
<td>--</td>
<td>C/T</td>
<td>T</td>
</tr>
<tr>
<td>8</td>
<td>rs16901979</td>
<td>8q24 (2)</td>
<td>128,194,098</td>
<td>--</td>
<td>A/C</td>
<td>A</td>
</tr>
<tr>
<td>8</td>
<td>rs16902094</td>
<td>8q24.21</td>
<td>128,389,528</td>
<td>--</td>
<td>N/A</td>
<td>G</td>
</tr>
<tr>
<td>8</td>
<td>rs620861</td>
<td>8q24 (4)</td>
<td>128,404,855</td>
<td>--</td>
<td>A/G</td>
<td>G</td>
</tr>
<tr>
<td>8</td>
<td>rs6983267</td>
<td>8q24 (3)</td>
<td>128,482,487</td>
<td>--</td>
<td>G/T</td>
<td>G</td>
</tr>
<tr>
<td>8</td>
<td>rs1447295</td>
<td>8q24 (1)</td>
<td>128,554,220</td>
<td>--</td>
<td>A/C</td>
<td>A</td>
</tr>
<tr>
<td>9</td>
<td>rs1571801</td>
<td>9q33</td>
<td>123,467,194</td>
<td>DAB2IC</td>
<td>G/A</td>
<td>A</td>
</tr>
<tr>
<td>10</td>
<td>rs10993994</td>
<td>10q11</td>
<td>51,219,502</td>
<td>MSMB</td>
<td>T/C</td>
<td>T</td>
</tr>
<tr>
<td>10</td>
<td>rs4962416</td>
<td>10q26</td>
<td>126,686,862</td>
<td>CTBP2</td>
<td>C/T</td>
<td>C</td>
</tr>
<tr>
<td>11</td>
<td>rs7127900</td>
<td>11p15.5</td>
<td>2,190,150</td>
<td>IGF2, IGF2AS, INS, TH</td>
<td>G/A</td>
<td>A</td>
</tr>
<tr>
<td>11</td>
<td>rs12418451</td>
<td>11q13 (2)</td>
<td>68,691,995</td>
<td>--</td>
<td>A/G</td>
<td>A</td>
</tr>
<tr>
<td>11</td>
<td>rs10896449</td>
<td>11q13 (1)</td>
<td>68,751,243</td>
<td>MYEOV</td>
<td>A/G</td>
<td>G</td>
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<tr>
<td>17</td>
<td>rs11649743</td>
<td>17q12 (2)</td>
<td>33,149,092</td>
<td>HNF1B</td>
<td>A/G</td>
<td>G</td>
</tr>
<tr>
<td>17</td>
<td>rs4430796</td>
<td>17q12 (1)</td>
<td>33,172,153</td>
<td>HNF1B</td>
<td>A/G</td>
<td>A</td>
</tr>
<tr>
<td>17</td>
<td>rs1859962</td>
<td>17q24.3</td>
<td>66,620,348</td>
<td>--</td>
<td>G/T</td>
<td>G</td>
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<tr>
<td>19</td>
<td>rs8102476</td>
<td>19q13.2</td>
<td>43,427,453</td>
<td>PPP1R14A</td>
<td>T/C</td>
<td>C</td>
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<td>19</td>
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<td>19q13</td>
<td>46,677,464</td>
<td>--</td>
<td>C/T</td>
<td>T</td>
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<tr>
<td>22</td>
<td>rs5945619</td>
<td>Xp11</td>
<td>51,258,412</td>
<td>NUDT10, NUDT11, LOC340602</td>
<td>C/T</td>
<td>C</td>
</tr>
</tbody>
</table>

While AUC has found widespread use in assessing predictive performance, a more fundamental question is whether the findings have clinical meaning. Unfortunately, AUC is an abstract value that has no inherent clinical meaning. While AUC assesses the ability of an assay to distinguish risk across all risk strata, is that really the goal? Rather,
in a clinical setting, the goal of such testing is typically to identify men at considerably elevated risk. Methods based on a risk cutoff, such as positive predictive value (PPV), offer more clinical meaning than AUC. A study that evaluated 28 PCa risk-associated SNPs within a Swedish population-based PCa case-control study (CAPS, Cancer of the Prostate in Sweden) found the PPV of this test was 36% when 3-fold increased risk over population median risk was used as a cutoff to define high risk [46]. This is comparable to PSA screening based on a 4 ng/mL cutoff [46]. This result has direct clinical meaning, as PPV is the disease detection rate among subjects predicted to be at risk based on this specific set of genetic risk markers. While AUC has merits as an objective measure of test performance that is well known in the field of public health and population screening, our results reinforce the view that AUC should not be viewed in isolation, but rather, in the context of other available measures, including PPV, that have more direct clinical relevance for the needs of patients and physicians.

Questions of health benefit

Even if GWAS SNPs allow accurate prediction of overall risk, and if the ethical concerns are addressed to some extent, questions of health benefit remain [47-50]. This is particularly important in a disease such as PCa, where most PCa tumors are not aggressive or life threatening, and thus treatment can cause more harm than good. Unfortunately, most GWAS SNPs identified to date are not associated with aggressiveness or survival, and are unable to predict these clinical features, leading to concerns for unnecessary biopsies, overdiagnosis, and overtreatment of indolent disease. This is not surprising, given the original studies primarily used early stage cases of PCa
for association discovery and validation. However, risk stratification might be sufficient to make a significant clinical impact. Prospective trials suggest that PSA-based over-detection of indolent PCa can be reduced by targeting PSA screening to higher risk patients.[3,4,13] This is illustrated by a recent analysis of the PLCO Cancer Screening Trial, showing PCa specific mortality can be reduced ~50% by targeting PSA screening to men with a positive family history (FH), a sharp contrast to the observation that PSA screening in the entire PLCO cohort increased PCa mortality by ~9% [51]. Multi-marker testing of GWAS SNPs has the potential to build on the risk estimation from FH, offering additional potential for risk stratification that can be used to target PSA screening. A recently published analysis of 9,404 PCa cases and 7,608 controls combined from three ongoing studies in the United Kingdom suggested that targeting screening to men at higher multi-marker genic risk could reduce overdiagnosis, with a 56% decrease in overdiagnosis between men in the lowest and the highest polygenic risk quartiles [52]. A similar study in Finnish men reached a similar conclusion, with a 21% decrease in overdiagnosis when comparing between men above versus below the mean risk as determined by multi-marker genetic testing for PCa [53]. In a retrospective analysis of a Swedish cohort of men who underwent a prostate biopsy between 2005 and 2007, use of a genetic prediction model that included PCa risk-associated SNPs and existing clinical variables (age, PSA, free-to-total PSA, and family history) would have led to significantly fewer biopsies (22.7%) than the non-genetic clinical model, at a cost of missing a PCa diagnosis in 3% of patients characterized as having an aggressive disease [54].
**Translational research framework: to the individual, clinic, and public health**

As described above, many of the technical and ethical arguments for and against the clinical application of multi-marker genetic testing have been addressed to some extent. For potential translation from the basic science laboratory bench to clinical care for patients, additional research is needed. In the following, we use prostate cancer to highlight a translational research (TR) framework that will allow us to capitalize upon the exciting results from multi-SNP tests and make a positive health impact. Research findings do not automatically jump from the lab to the clinic, and rather TR can be envisioned as a series of intermediate phases that comprise TR [55-60]. Applied to Genomics, TR stages will often include; T1) confirm association and establish clinical validity; T2) evaluate clinical utility; T3) conduct practice-based implementation research; and finally T4) population/community wide outcomes assessment.

To date, most of the studies following up on GWAS findings have emphasized T1. After initial discovery of candidate associations, the goal of T1 is to minimize the possibility of spurious associations. Statistical concerns are primarily addressed by utilizing independent populations with large numbers of samples for confirmation analyses, reducing the possibility of false positives due to chance. Prospective studies may be needed to assess clinical sources of spurious association that are difficult to address in case-control studies, such as for PSA detection bias. T1 research aims to answer questions such as, “Are these SNPs truly associated with PCa, and not with PSA levels that lead to the detection of most PCa cases?” By answering this type of question, we can establish the validity of associations.
To examine whether the valid associations from T1 have clinical utility, T2 research includes prospective studies, either observational or interventional (clinical trials), and comparative effectiveness research (CER). Unfortunately, very few of the initially promising associations are tested in prospective studies that can pave the way through the T2 phase [60-61], in part because prospective studies are costly and require many years. One efficient approach is to utilize previously completed prospective studies by examining predictors at baseline (e.g. clinical parameters and genotypes) in relation to outcome data. This approach is particularly appropriate for genetic studies in which genetic markers are effectively blinded to patients and observers, reducing potential bias. Another approach to T2 is CER, defined by the Institute of Medicine as, “The generation and synthesis of evidence that compares the benefits and harms of alternative methods to prevent, diagnose, treat, and monitor a clinical condition or to improve the delivery of care” [62]. By comparing multi-marker genomics tests to existing clinical markers such as family history and PSA screening, CER gives clinical meaning to statistical associations. T2 research hopes to answer questions such as “How does the PPV of a combined SNP test for PCa risk compare to the PPV of family history or PSA?” Clear answers to these types of questions can inform the subsequent development of professional guidelines, policy, and clinical use.

T3 research examines the practical issues impacting clinical usage, thus seeking to maximize the utility that is established by T2 research. T3 studies might evaluate physician motivation to offer tests, patient uptake of tests, patient interpretation of results,
physician recommendations based on test results, and any downstream decisions of those receiving test results. T3 research may also explore the differential impact when testing is applied in different clinical settings from private practice to specialty clinics or academic centers. Initial cost effectiveness analysis, utilizing data gathered in specific clinical settings, may occur in conjunction with T3, in an effort to predict the costs of more widespread clinical implementation. Another area for T3 research is the evaluation of various implementation scenarios, such as population screening versus just targeting the testing to high risk families. Questions addressed by T3 research might include, “Do genomic test results for PCa risk alter perception and accordingly patterns of PSA screening?”

Following the introduction of a new intervention, T4 research focuses on health outcomes amongst communities. Rather than the well-defined groups of patients studied in T3 research, T4 monitors the real world impact. For example, when new genomic tests are introduced, population based registries may be used to observe disease incidence; if a decrease in incidence or mortality is observed, then this may be attributable to the test, particularly if evidence from T1 through T3 would predict the observed effect in absence of other significant factors. Formal cost effectiveness analysis may be another important component of T4, utilizing real world data on cost, test usage, and outcomes. Questions addressed in T4 could include “Following the widespread introduction of a new genomic risk assessment test, how many cases of PCa are prevented in a population, and at what financial cost?” By answering these questions, it is possible to monitor whether the test is having the effects that were expected based on results of T1-T3 research. Projects
funded by the National Cancer Institute have been heavily skewed toward the discovery phase, or T1 of TR [60-61]. If we are to reap the full benefit of the heavy investment in discovery approaches such as GWAS, then it is imperative that scientists and clinicians commit to carrying out T2, T3, and T4 research.

**Hypothesis and approach**

This thesis is based on the hypothesis that multi-marker genetic testing for PCa risk is safe and effective for use by patients and clinicians. Again, the aims of this work were:

**Aim 1.** To compare the provision Family History (FH) versus Genetic Risk Score (GRS) for Prostate Cancer (PCa) risk from the perspective of at-risk patients.

**Aim 2.** To evaluate whether a short educational intervention can address key barriers to clinical implementation of GRS among primary care providers.

Chapter II contains a manuscript that addresses Aim 1, which is practice based clinical research to evaluate practical issues at stages T2 and T3 of a translational research framework. This was accomplished by a new prospective randomized clinical trial to assess the impact of the SNP panel on risk perception and behavioral outcomes. Subject recruitment in the trial consisted of men age 40 to 49 years, Caucasian, and never had prior PSA screening or PCa diagnosis. Baseline surveys collected data on their perception of PCa risk, numeracy, and health attitudes. Subjects were randomized, with half to receive a standard risk assessment (family history and age), and the other half to receive a risk assessment based on SNPs plus standard risk assessment. Immediately
following the disclosure of the risk assessment based on these two methods, we assessed recall and the perception of risk in each group. After three months we evaluated behavior outcomes such as discussion of results with family members, engaging in medical appointments, discussion of PCa screening options with a medical provider, engaging in PCa screening such as PSA, and uptake of preventative measures such as chemoprevention. Three years later, we assessed medical records for uptake of PSA screening. By comparing the two randomization groups, we were able to measure the impact of the SNP panel on risk perception and behavioral outcomes. We also evaluated the effect of different levels of risk information that were provided to participants within each group.

Chapter III contains a manuscript that addresses Aim 2. Primary care providers (PCP) have been surveyed extensively regarding genetics knowledge and confidence, showing that they are competent and confident regarding many basic genetics concepts; however, significant barriers remain with regard to implementation of multi-marker testing. We conducted a T3 study that assessed a 15-minute continuing medical education session to improve PCP understanding and confidence regarding genetic testing, using multi-marker genomic testing for prostate cancer as an example. We collected pre- and post- surveys from 45 PCPs to evaluate changes in knowledge and confidence.
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CHAPTER II

RANDOMIZED TRIAL FINDS PROSTATE CANCER GENETIC RISK SCORE FEEDBACK TARGETS PSA SCREENING AMONG AT-RISK MEN

Manuscript accepted by: Cancer

Title: Randomized trial finds Prostate Cancer Genetic Risk Score Feedback Targets PSA Screening Among At-Risk Men

Short running title: Genetic Risk Score Targets PSA Screening

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Trial Registration: clinicaltrials.gov, NCT02381015.

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Precis: This prospective trial found that provision of individual genetic risk scores for prostate cancer did not lead to significant increases in anxiety or use of PSA screening. Rather, genetic risk scores led to targeted use of PSA screening among higher risk men, which may improve PSA screening performance.

Author contributions: The study was design was led by J.X., with significant input and revision from R.J.K., A.K.K., S.L.Z., W.B., A.R.T., and B.R.L. The study design was implemented as an approved functional protocol by D.R., A.R.T., B.R.L., H.T., T.A.,
Z.Z., I.L., T.Mck., S.Z., and A.K.K. Recruitment and data work (collection, entry, and checks) were performed by D.R., S.N., T.A., H.T. T.M., T.Mck., T.Y., R.R., W.B., Z.Z., A.R.T., and B.R.L. Laboratory assays and associated quality control were designed and conducted by T.Y., S.Z, and T.M. Risk reports were generated and checked by A.R.T., T.Y., T.Y., T.M., and S.Z. Data analysis was conducted by A.R.T. under supervision of Z.Z. and F.H. All authors assisted with interpretation of the results. Individual sections of the manuscript were drafted by A.R.T., B.R.L., D.R., S.N., and I.L. First complete draft of the manuscript was assembled by A.R.T. and B.R.L. Significant conceptual and technical revision and additions to the manuscript was provided by all co-authors. Final review and approval of the manuscript was provided by all co-authors. A.R.T. and B.R.L. had full access to all the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis.
Abstract

Background

Prostate-specific antigen (PSA) screening may reduce death from prostate cancer (PC), but leads to overdiagnosis of many cases of indolent cancer. Targeted use of PSA screening may reduce overdiagnosis. Multi-marker genomic testing shows promise for risk assessment, and could be used to target PSA screening.

Methods

To test whether counseling based on family history (FH) versus counseling based on Genetic Risk Score (GRS)+FH differentially affects subsequent Prostate Specific Antigen (PSA) screening at 3 months (primary outcome), we conducted a randomized trial of FH vs. GRS+FH was conducted in 700 Caucasians aged 40-49 years without prior PSA screening. Secondary outcomes included anxiety, recall, physician discussion at three months, and PSA screening at 3 years. We also evaluated pictographs versus numeric presentations of genetic risk.

Results

At three months, no significant differences were observed in rates of PSA screening between FH (2.1%) and GRS+FH (4.5%) arms (x²=3.13, p=0.077); however, PSA screening rates at three months significantly increased with given risk in the GRS+FH arm (p=0.013). Similar results were observed for discussion with physician at three months and PSA screening at three years. Average anxiety levels decreased after providing individual cancer risk (p=0.0007), with no differences between groups. Visual presentation by pictographs did not significantly alter comprehension or anxiety.
Conclusion

This is likely the first randomized trial of multi-marker genomic testing to report genomic-targeting of cancer screening. We found little evidence of concerns for excess anxiety or over/under use of PSA screening when providing multi-marker genetic risks to patients.

Key Words: Randomized Controlled Trial, Prostate Cancer, Genetic Risk Score, Genetic Testing, PSA Screening, Genetic Counseling
Introduction

The United States Preventive Services Task Force recommends against routine Prostate-Specific Antigen (PSA) screening, citing risks of over-diagnosis and over-treatment\(^1\). The American Cancer Society (ACS), American Urological Association (AUA), and European Association of Urology (EAU) maintain that PSA screening should be considered after physician-patient discussion, and earlier age screening (<age 55 years) should be offered to men at increased risk (e.g. positive family history)\(^2\,3\,4\). Prospective trials suggest that a favorable balance of risks and benefits can be achieved by targeting PSA screening to higher risk patients.\(^5\,6\,7\)

Family history (FH) risk assessment is an established approach that enables targeted PCa screening in clinical settings, and is actively promoted by The Centers for Disease Control and The US Surgeon General.\(^8\,9\) Genetic Risk Score (GRS) is a new approach to determine individual risk that builds on family history by assessing single nucleotide polymorphisms (SNPs) associated with PCa risk.\(^10\,14\) The clinical validity and utility of risk prediction using GRS has been demonstrated in large prospective studies.\(^15\,16\)

However, there are concerns for clinical application of GRS, including increased anxiety and avoidance or overuse of medical care.\(^17\,20\) In consideration of these concerns, we studied a specific application of GRS plus FH, for personalized risk assessment of PCa, and evaluated the potential for targeted Prostate Specific Antigen (PSA) screening.
Methods

Design

We conducted a prospective, randomized-controlled study primarily comparing the impact of GRS+FH versus FH risk feedback information on PSA screening rates as the primary outcome. Secondary outcomes included discussion of PSA screening with a physician and subject anxiety. We also compared anxiety and PCa risk recall for numeric versus pictograph presentations of this risk feedback for a 2x2 matrix of 4 randomization groups. Prior studies suggested pictographs increase comprehension and reduce worry.\textsuperscript{21} The design and data collection timepoints are shown in Figure II-1.

Randomization

Computerized randomization of 700 study IDs into 175 blocks of four each was completed prior to study enrollment, ensuring subjects were continuously randomized into the four groups during the recruitment timeframe. The randomization list was kept at Wake Forest, and not available to the enrollment team in Michigan. This process masked randomization status until the risk report was provided to each participant.

Randomization groups were (Group 1) GRS+FH as a number; (Group 2) GRS+FH as a number and pictograph; (Group 3) FH as a number; and (Group 4) FH as a number and pictograph.
Enrollment

Recruiters worked with primary care offices in West Michigan (Spectrum Health Medical Group and Grand Valley Medical Specialists) to query patient databases for qualified patients from June 2011 through February 2012. Potential participants were screened...
over the phone or in person and qualified individuals received detailed information about undergoing genetic testing for PCa and randomization details as part of the study informed consent process. Each subject was offered personalized risk feedback and up to $80 compensation if they completed the trial.

Eligibility criteria were age 40 to 49 years, self-defined Caucasian background, and no prior PSA screening nor PCa diagnosis. These criteria helped ensure inclusion of high-risk men that were PSA-naïve, and were consistent with ACS and AUA guidelines for earlier offer of screening for men at increased risk. Participation was limited to Caucasians due to lacking information regarding risk prediction with these genetic markers in other races/ethnicities at the time of study startup. Informed consent was documented in writing. Prior to enrollment, this study was approved by institutional review boards at each participating institution.

Data collection and study participation

At baseline, participants completed the State-Trait Anxiety Inventory and donated saliva samples (Oragene, Inc). A CLIA-certified lab at Spectrum Health Hospital in Grand Rapids Michigan assayed a validated panel of 46 SNPs. A report for lifetime risk of PCa was generated for each subject (Supplemental Figure II-1). The report content and format was based on the 4 randomization groups. Participants in the FH arm were given lifetime PCa risks of either 17% or 23% based on negative or positive family history (Figure II-2a), respectively, based on the estimated OR for FH, calibrated incidence rates, and mortality rates excluding PCa as derived from SEERS data. In the GRS+FH arm, risk calculations included the SEERS-derived FH+/- risk and a sum of the estimated OR for each SNP, resulting in risks that were distributed more broadly (Figure II-2b) based
on the number of risk alleles.\textsuperscript{12,22} Four to six weeks after baseline, participants met with a certified genetic counselor to receive their personal risk report and complete survey measures. At the three-month phone survey, participants repeated survey measures, with new questions about behaviors following the intervention, including further discussion of PCa screening with their PCP and PSA screening. Electronic medical records of all subjects were queried for PSA screening (median: 3.02 years).

\textbf{Figure II-2. Distribution of Genetic Risk Scores Given to Study Participants}

\textbf{Figure II-2a. Family History Group}
All participants were asked to donate saliva samples (Oragene, Inc) to maintain the blind status of participants until the results were disclosed. All saliva samples and data were labeled with unique study identifiers to protect confidentiality. Samples were transported to a CLIA-certified laboratory at Spectrum Health for DNA isolation and SNP genotyping. The lab assayed a validated panel of 46 SNPs, consisting of 33 analytical SNPs and 13 built-in quality controls and duplicated SNPs. The design of this panel was based on prior published research by our study team, with SNPs drawn from the results of prior GWAS and confirmation studies in Caucasian populations (p-value <1.0×10^{-6}) and limited to one SNP from each independent LD block. The Illumina BeadXpress Reader was selected for genotyping based on several factors, namely the 96 well format that allowed a total of 48 samples and controls to be processed in duplicate, ability to
multiplex (simultaneous genotype) the 46 selected SNPs per sample, and FDA clearance for in vitro diagnostics. De-identified SNP genotyping results were then sent from the lab at Spectrum Health to the Wake Forest team for risk report generation.

The Wake Forest team subsequently generated a de-identified risk report for each subject, containing the estimated lifetime risk for PCa and a description of factors comprising this risk (Supplemental Figure II-1). The content and format of these reports were based on the 4 randomization groups. Pictographs were included in half of the risk reports and were based on a pictograph generator from the University of Michigan. Participants who responded “no” or “do not know” for FH of prostate cancer were classified as having a negative family history. Absolute risk was calculated using the method we have described previously, which is based on the SNP-specific RR, calibrated incidence rate of PCa, and mortality rate for all causes excluding PCa in the U.S. Risks greater than 80% were reported as 80% due to concerns about stability of estimates above that point. The risk reports were then transmitted via a secure study website to the study team in Michigan in preparation for visit two. The study coordinator in Michigan linked the study ID back to personal identifiers, added these identifiers, and then finalized the re-identified risk report.

Genetic counseling.

Genetic counselors followed prepared scripts at study intake and when disclosing results. All deviations/unexpected questions were recorded. Each subject was given a copy of a Centers for Disease Control brochure on PCa screening, and provided with a resource card for more information (Supplemental Figures II-4 and II-5).
Measures

The State-Trait Anxiety Inventory (STAI) is a validated assessment tool that has been used extensively in both clinical and research settings to measure anxiety. It comprises separate self-report scales for measuring state and trait anxiety. In order to measure changes in anxiety at three study timepoints, we utilized the S-Anxiety scale (State Anxiety). The S-Anxiety scale assesses current feelings “at this moment”: 1) not at all, 2) somewhat, 3) moderately so, and 4) very much so. While the full S-Anxiety scale includes 20 items, we utilized a shortened version, consisting of ten items (Questions 1, 3, 5, 9, 11, 12, 13, 15, 17, and 19) from the STAI Form X1. This subset of items has been used in prior studies by members of the study team. Each item within the STAI is scored on a scale of 1 to 4, so with ten items the possible range of total scores would be from 10 (lowest anxiety) to 40 (highest anxiety) for each participant. To identify anxiety levels of potential clinical importance, we utilized a pro-rated S-Anxiety score threshold equal to 41 or greater (i.e. threshold=20.5 on scale of 10-40); this threshold was selected based on gender and age-specific normative data in STAI manual, and then setting a cutoff 0.5 S.D. above the respective mean. The STAI was assessed at baseline, immediately pre-result, immediately post-result, and at 3 month follow-up.
Risk recall was assessed immediately post result, by the question:

- “Based on the information given to you, what were you told is your chance of developing prostate cancer in your lifetime from 0-100%?” [fill in the blank]

At the 3 month follow-up, behavioral outcomes were assessed by the following questions:

- “Since we last spoke to you, have you talked to a doctor about having a PSA test to further determine your chance of having prostate cancer?” [yes or no]
- “Since we last spoke to you, did you have a PSA test performed?” [yes or no]

**Statistical analyses**

The primary outcome was self-reported PSA screening by 3 months. Secondary outcomes included: 1) State-Trait Anxiety Inventory (immediate pre/post), 2) risk recall (immediate post, 3 months), 3) discussion with a physician regarding PSA screening by 3 months, and 4) medical record confirmed PSA screening by 3 years. We assessed main effects for risk type [GRS+FH (Groups 1 and 2) versus FH (Groups 3 and 4)]. Non-parametric one-way ANOVA was used to compare continuous data across groups. Fisher’s exact test or chi-square test were used to evaluate associations between categorical measures and groups. Associations between risk estimates provided to subjects and continuous or binary outcomes were tested using linear (recall) or logistic (physician discussion, and had PSA screening) regression, respectively. Repeated measures (anxiety) were evaluated using Wilcoxon signed-rank tests. Statistical analyses were performed using SAS 9.2.
Results

Sample Characteristics

700 patients were enrolled and 97.4% completed the 3-month follow-up. During 3 years of follow-up by medical records, 70.3% were positively observed to receive any health care subsequent to study participation, such as clinic visits or labwork (Figure II-1). The demographic distributions suggest randomization resulted in four groups with similar characteristics (Table II-1). The average participant was age 45 years, had annual income of $50,000 to $100,000 (46%), a college graduate (45%), married (76%), and a negative first degree FH (91.2%, including 14% in whom FH was unknown).
Table II-1. Subject demographics by randomization group.

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<th>RANDOMIZATION GROUP</th>
<th>GRS-number</th>
<th>GRS-pict</th>
<th>FH-number</th>
<th>FH-pict</th>
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<td>175</td>
<td>175</td>
<td>175</td>
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<td>Completed visit 2</td>
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<td>168</td>
<td>173</td>
<td>169</td>
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<tr>
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<td>Medical records observation during 3 yrs. follow-up</td>
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<td>134</td>
<td>115</td>
<td>118</td>
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<td>44.8</td>
<td>44.7</td>
<td>45.0</td>
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<td></td>
<td>(2.85)</td>
<td>(3.06)</td>
<td>(2.84)</td>
<td>(2.76)</td>
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<td>Annual Income in U.S.D (%)</td>
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<td>3</td>
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<td>7</td>
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<td>Education (%)</td>
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<td>9</td>
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<tr>
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<td>17</td>
<td>19</td>
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<td></td>
<td>% declined</td>
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<td>0.6</td>
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<td>0</td>
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<td>13</td>
<td>11</td>
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<tr>
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<td>13</td>
<td>10</td>
<td>13</td>
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<tr>
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<td>14</td>
<td>6</td>
<td>10</td>
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</table>

* t-tests for continuous data, and Fisher’s exact tests for categorical data.
PSA Discussions and Screening by Group

Three months after risk counseling, 16.3% (n=111 of 681) of participants reported discussion of PSA screening with a physician, and 3.25% (n=22 of 677) reported having PSA screening (Supplemental Table II-1). For the primary outcome, no significant differences were observed in the rate of PSA screening at three months across by type of feedback (GRS+FH versus FH, x²=3.13, p=0.077); similar non-significant results were seen when comparing across all four randomization groups (x²=3.25, p=0.35), and by format of risk feedback (NM versus PT, x²=0.13, p=0.72) (Supplemental Table II-1).

Similarly, physician discussion did not vary significantly between all four randomization groups (x²=3.78, p=0.29), by type of feedback (GRS+FH versus FH, x²=3.41, p=0.065) or by format of feedback (NM versus PT, x²=0.37, p=0.54) (Supplemental Table II-1).

Three years after results disclosure, medical records showed 33% (n=160 of 492) of participants had undergone PSA screening. This rate of PSA screening at three years did not significantly vary between all four randomization groups (x²=3.78, p=0.29), by type of feedback (GRS+FH versus FH, x²=1.7, p=0.19) or based on format of the risk feedback (NM versus PT, x²=0.61, p=0.44) (Supplemental Table II-1).

Effects of Lifetime PCa Risk on Anxiety, PSA Discussions, & Screening

In the GRS+FH arm, as participants were given increased lifetime PCa risks, they were significantly more likely to report PSA discussion with a physician by three months (Wald x²=9.11, p=0.0025) (Figure II-3a), engage in PSA screening by three months (Wald x²=6.13, p=0.013) (Figure II-3b), and engage in PSA screening by three years (Wald x²=9.7, p=0.0018) (Figure II-3c) (Supplemental Table II-2). For example, among
men whose given PCa risk were <1, 1-2, 2-3, and >3-fold higher than population average, we observed 2.7%, 4.8%, 9.4%, and 16.7% of these men elected PSA screening by three months, respectively. Among subjects with a negative family history in the GRS+FH arm (n=229), given risk was significantly associated with PSA screening (n=77, 33.6%) at 3 years (Wald $\chi^2=8.9$, p=0.0027). In contrast, none of these outcome trends for PSA screening and physician discussion were observed in the FH arm (Figure II-3a-c and Supplemental Table II-2).
Figure II-3. Participant health behaviors, in FH and GRS arms, stratified by given risk.

a. Discussed PSA screening with physician per self-report during 3 month follow-up

b. Engaged in PSA screening per self-report during 3 month follow-up

c. Engaged in PSA screening, per medical record review, during 3 years of follow-up
Post-result anxiety was positively related to given risk, with a significant linear relationship in the GRS+FH feedback arm ($\beta=10.6$, s.e.$=1.77$, $t=5.97$, $p=<0.0001$) but not the FH feedback arm ($\beta=19.1$, s.e.$=13.7$, $t=1.39$, $p=0.16$) (Supplemental Figure II-2). Given risk was significantly associated with post-result anxiety levels indicative of clinical importance (STAI S-Score pro-rated cutoff of 41 or greater$^{24,25}$) in the GRS+FH arm (Wald $x^2=24.9$, $p<0.0001$), but not in the FH arm (Wald $x^2=2.77$, $p=0.09$).

**Post-Result Anxiety and Pre-Post Change in Anxiety by Group**

Immediate post-result anxiety did not significantly differ by randomization group ($x^2=2.39$, $p=0.49$), by feedback type (GRS+FH versus FH, $x^2=0.93$, $p=0.34$) or format (NM versus PT, $x^2=1.46$, $p=0.23$) of risk feedback (Supplemental Table II-3). From immediate pre-result (mean=15.66) to immediate post-result (mean=15.31), the average anxiety score for the complete study sample decreased significantly ($S=-11660$, $p=0.0007$) (Supplemental Table II-3). The change in anxiety scores did not vary significantly across all four randomization groups ($x^2=2.18$, $p=0.54$), by feedback type (GRS+FH versus FH, $x^2=0.93$, $p=0.33$) or risk feedback format (NM versus PT, $x^2=0.081$, $p=0.78$) (Supplemental Table II-3). Although no group differences were observed in baseline anxiety level (Supplemental Table II-3), we ran linear regression adjusting for baseline and still observed no group differences in pre-post anxiety.

When anxiety levels indicative of clinical concern were evaluated (STAI S-Score pro-rated cutoff of 41 or greater$^{24,25}$), group differences were observed in the number of subjects with clinically important anxiety level at baseline; linear regression adjusting for...
baseline anxiety showed no group differences in post result clinically important anxiety. Comparing the 104 subjects that exceeded this threshold post-results versus the remaining 590 subjects, there was no significant difference in rate of PSA discussion with a physician by three months ($x^2=0.018$, $p=0.89$) or engaging in PSA screening by three months ($x^2=0.018$, $p=0.89$) (Figure II-3b); however, this subset of subjects was significantly more likely to engage in PSA screening by three years ($x^2=3.99$, $p=0.046$). Regression analysis adjusting for baseline showed no significant relationship between post result clinically important anxiety and post-result PSA screening by three years.

Recall of Risk

As a measure of comprehension, we evaluated recall of the risk given to subjects (i.e. given risk). We observed a significant linear relationship between given risk and recalled risk at the immediate post-results assessment ($\beta=93.5$, s.e.=1.55, $t=60.2$, $p<0.0001$) (Supplemental Figure II-3a), and at the 3-month follow-up assessment ($\beta=94.7$, s.e.=2.93, $t=32.4$, $p<0.0001$) (Supplemental Figure II-3b). At both assessments, the relationship between given risk and recall was significant in each of the four randomization groups ($p<0.001$).

Discussion

The prospective, randomized study design allowed for comparison of counseling regarding individual lifetime risk of PCa based on GRS+FH vs. FH. We found no significant differences in the overall rate of PSA screening (3% at 3 months, 23% by 3 years) between study groups after risk assessment, suggesting neither the source of risk feedback (genetic or family history) nor the presentation format (numerical only or
numerical plus pictograph) were important determinants of subsequent screening behavior. The level of given risk in the GRS+FH arm was a significant determinant of screening behavior. At 3 months, participants in the GRS+FH arm that were given >3-fold greater risk were 2.2 times more likely to discuss PSA screening with a physician, and 3.8 times more likely to engage in PSA screening compared with those given average risk, providing evidence of increased screening utilization among individuals that were given higher-risks. Similar trends were observed upon review of 3-year medical record data. Our observation that given risk was significantly associated with PSA screening at 3 years among subjects with a negative family history in the GRS+FH arm further underscores the potential for GRS+FH to target PSA screening amongst a group of men typically considered at uniformly low risk. These observations of genomic-targeted PSA screening are important in light of the PSA screening debate. Several current screening guidelines recommend targeted application of PSA screening; we now provide new evidence of effective genomic targeting of PSA tests. Our results also address patient-centered concerns for clinical application of GRS+FH, including the potential for increased anxiety and avoidance or overuse of medical care.\textsuperscript{17-20}

A prior multi-marker genetic risk assessment study reported no differences in diet, exercise, or use of screening tests, from baseline to 5.6 months average follow-up.\textsuperscript{20} Another recent randomized trial of genetic and environmental risk assessment for colorectal cancer did not observe screening differences within six months by group or given risk level.\textsuperscript{26} That study utilized subjects that were already non-compliant with screening, whereas we focused on screening-naïve subjects. The present study is likely the first prospective randomized trial to observe screening behavior changes, confirmed
by medical records, in response to multi-marker genetic risk feedback in an average-risk population. Our findings of targeted screening are similar to prior studies of high-penetration genes, with changes in mammography rate following disclosure of BRCA1 results.27,28 and in colonoscopy associated with HNPCC genes.29 The finding of behavioral change associated with increasing risk in the GRS+FH arm may reflect a combination of a prospective randomized design, large study population, retention of 97% participants until 3 month follow-up, confirmed medical record observations on 70% by three years, focus on PCa, prediction of cancer risk, characteristics of the study population, and the broad spectrum of risk stratification.

Studies of hereditary PCa have shown that risk increases with additional affected family members30-32. Despite this, we are not aware of clinical guidelines for PCa risk estimation based on family history. Current clinical guidelines for PSA screening (AUA, ACS, EAU) and prior large prospective studies have considered FH as either positive or negative. Accordingly, FH risk estimates were binary in the present study, 17% negative versus 23% positive. This binary approach allowed for accurate and stable risk estimates to all subjects, while reflecting the binary FH risk assessment used in the primary care settings where PSA screening occurs. Unfortunately, binary FH risk assessment limits risk stratification, and as seen in our study, limits the potential to motivate behavior change. GRS+FH adds information from genetic markers to FH, distributing risk from 0% to 80% in this study. The importance of the larger range of risk feedback from GRS+FH is highlighted by our observation that the level of given risk was critical in explaining screening behaviors in the GRS+FH arm. In light of our findings, clinicians and future studies should consider incremental rather than binary assessment of family
history risk for PCa. In this regard, development of clinical guidelines for incremental FH risk assessment for PCa may be helpful in terms of establishing a standard.

Regardless, FH and GRS+FH are complimentary, neither is diagnostic, and both can stratify risk to enable targeted screening. GRS+FH could reduce misclassification of risk for patients in which FH is negative (77% in the present study) or not available (14% in the present study). 33-36

Based on our results, a subset of patients will experience clinically important levels of anxiety in connection with the disclosure of risk feedback; clinicians and laboratories should therefore ensure individuals who undergo risk assessment and testing receive adequate pre- and post-results counseling. Overall, the provision of risk feedback led to statistically significant decreases in average anxiety, consistent with genetic testing studies of colon cancer and Alzheimer’s disease. 26,29,37 The provided risk feedback was accurately recalled, and anxiety modestly increased (although not clinically relevant) in direct proportion to given risk, similar to previous multi-marker genetic studies. 20,38

These findings add to the evidence suggesting concerns of providing multi-marker genetic feedback to patients may be over-estimated.

The lack of differences in recall associated with format of risk feedback conflicts with findings from several prior studies that indicated pictographs are a superior method to convey risk feedback to patients across all numeracy levels. 21 However, much of the prior work in risk communication has utilized hypothetical scenarios in controlled laboratory studies rather than personal risk results delivered to patients in clinical settings. 39 A recent empiric study on communication of breast cancer risks is consistent with our findings of no observable benefit in recall when using pictographs to communicate risk. 39
Given that clinical genetic results are conveyed in a variety of formats, our findings may help inform clinical practices in risk communication, as well as future research. Perhaps there is no single approach for the communication of genetic risks that is beneficial across all numeracy levels and in all settings; in this case, it will be crucial to identify subsets of patients and clinical settings in which different methods have measurable benefit.

Limitations of this study include the inability to evaluate PCa detection rates and outcomes of PCa treatment based on low (expected) event rate during the follow-up period. Demographic features of the study population may limit generalization. Some subjects were lost to follow-up, although intent-to-treat analysis utilizing all 700 subjects yielded similar results for major outcomes. Current validated SNPs and/or FH are believed predictive of any PCa rather than high-grade PCa; coupled with PSA screening, this may lead to increased diagnosis of early stage PCa that would never require treatment, and is worth long-term study. Despite the limitations, these results indicate how genetic testing results are perceived and acted upon.

In summary, in this prospective RCT of 700 men, provision of individual GRS+FH did not lead to significant increases in anxiety or use of PSA screening. Rather, GRS+FH led to targeted use of PSA screening among higher risk men, which may improve PSA screening performance.
Acknowledgements

We thank the collaborating institutions and their supportive staff at Wake Forest School of Medicine, ClinXus, Van Andel Research Institute, Spectrum Health, and Grand Valley Medical Specialists. Also, thanks to Kevin McCormick, MD and George Bruins, MD and their staff at their respective Spectrum Health Medical Group offices for assistance in recruitment efforts.

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   AND


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Figure Legends.

Figure II-1. Study design, enrollment, and outcomes.

Figure II-2. Distribution of Genetic Risk Scores Given to Study Participants in FH (A) and GRS+FH (B) arms. Red bars represent the percentage of participants given a specific risk value. Black dashed line at 18.3% represents the average risk that was also provided on each participant risk report.

Figure II-3. Participant health behaviors, in FH and GRS+FH arms, stratified by given risk. Black bars represent the percentage of participants that reported engaging in health behaviors during three month follow-up. Blue bars represent these same percentages, but stratified by category of given risk.

a. Discussed PSA screening with physician per self-report during 3 month follow-up.

b. Engaged in PSA screening per self-report during 3 month follow-up.

c. Engaged in PSA screening, per medical record review, during 3 years of follow-up.
Supplemental Materials.

1. Supplemental Figure II-1a. Risk report template for participants randomized to receive risk results based on genetic risk score in numeric format.

2. Supplemental Figure II-1b. Risk report template for participants randomized to receive risk results based on genetic risk score in pictograph format.

3. Supplemental Figure II-1c. Risk report template for participants randomized to receive risk results based on family history in numeric format.

4. Supplemental Figure II-1d. Risk report template for participants randomized to receive risk results based on family history in pictograph format.

5. Supplemental Figure II-2. Risk Given to Participants is positively related to Risk Recall.

6. Supplemental Figure II-2a. Linear relationship of Given Risk with Risk Recall Immediately Following Results Disclosure

7. Supplemental Figure II-2b. Linear relationship of Given Risk with Risk Recall 3 Months Following Results Disclosure

8. Supplemental Figure II-3. Risk given to participants is positive and linearly related to post-result anxiety among participants who received risk feedback based on genetic risk score information

9. Supplemental Figure II-4. Text of Study Resource Card, as given to all study participants during study visit 2.

10. Supplemental Figure II-5. Prostate Screening Brochure from Centers for Disease Control, as given to all study participants during study visit 2.

11. Supplemental Table II-1. Average anxiety pre- and post-results

12. Supplemental Table II-2. Comparison of behavioral outcomes between groups.

13. Supplemental Table II-3. Relationship between given risk and behavioral outcomes within each randomization group.
Supplemental Figure II-1a. Risk report template for participants randomized to receive risk results based on genetic risk score in numeric format.

Prostate cancer risk assessment report

Patient

Subject Number: GO-1000  
Name: John Smith  
Age (DOB): 45 (8-12-1965)  
Race: Caucasian  
Family history Prostate Cancer: None reported

The patient reported the above clinical information regarding age, race, and family history. In addition, the patient underwent genetic testing to determine susceptibility for prostate cancer (PCa). This report was generated as part of a research study on prostate cancer risk assessment, as a collaboration of Spectrum Health, Van Andel Research Institute, Wake Forest University, and Duke University.

RISK ESTIMATE for PCa:

Based on age, race, family history, and genetic testing result information, the overall lifetime risk of prostate cancer for this patient is 17%. This means that out of 100 men with the same risk profile, we expect on average 17 to develop prostate cancer in their lifetime.

For comparison, the lifetime risk of PCa is 18.3% for the average U.S. man (from age 40 to 79).

RECOMMENDATION:

It is recommended that these results be conveyed to the patient by a qualified provider, including a discussion of follow-up options that are appropriate based on the overall clinical status.
Supplemental Figure II-1b. Risk report template for participants randomized to receive risk results based on genetic risk score in pictograph format.

Prostate cancer risk assessment report

Patient
Subject Number: GO-1000
Name: John Smith
Age (DOB): 45 (8-12-1965)
Race: Caucasian
Family history Prostate Cancer: None reported

The patient reported the above clinical information regarding age, race, and family history. In addition, the patient underwent genetic testing to determine susceptibility for prostate cancer (PCa). This report was generated as part of a research study on prostate cancer risk assessment, as a collaboration of Spectrum Health, Van Andel Research Institute, Wake Forest University, and Duke University.

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For comparison, the lifetime risk of PCa is 18.3% for the average U.S. man (from age 40 to 79).

RECOMMENDATION:
It is recommended that these results be conveyed to the patient by a qualified provider, including a discussion of follow-up options that are appropriate based on the overall clinical status.
Supplemental Figure II-1c. Risk report template for participants randomized to receive risk results based on family history in numeric format.

**Prostate cancer risk assessment report**

**Patient**

Subject Number: GO-1000  
Name: John Smith  
Age (DOB): 45 (8-12-1965)  
Race: Caucasian  
Family history Prostate Cancer: None reported

The patient reported the above clinical information regarding age, race, and family history. This report was generated as part of a research study on prostate cancer risk assessment, as a collaboration of Spectrum Health, Van Andel Research Institute, Wake Forest University, and Duke University.

RISK ESTIMATE for PCA:

Based on age, race, and family history, the overall lifetime risk of prostate cancer for this patient is 17%. This means that out of 100 men with the same risk profile, we expect 17 to develop prostate cancer in their lifetime.

For comparison, the lifetime risk of PCA is 18.3% for the average U.S. man (from age 40 to 79).

RECOMMENDATION:

It is recommended that these results be conveyed to the patient by a qualified provider, including a discussion of follow-up options that are appropriate based on the overall clinical status.
Supplemental Figure II-1d. Risk report template for participants randomized to receive risk results based on family history in pictograph format.

**Prostate cancer risk assessment report**

**Patient**

- **Subject Number:** GO-1000
- **Name:** John Smith
- **Age (DOB):** 45 (8-12-1965)
- **Race:** Caucasian
- **Family history Prostate Cancer:** None reported

The patient reported the above clinical information regarding age, race, and family history. This report was generated as part of a research study on prostate cancer risk assessment, as a collaboration of Spectrum Health, Van Andel Research Institute, Wake Forest University, and Duke University.

**RISK ESTIMATE for PCA:**

Based on age, race, and family history, the overall lifetime risk of prostate cancer for this patient is **17%**. This means that out of 100 men with the same risk profile, we expect 17 to develop prostate cancer in their lifetime (see figure).

For comparison, the lifetime risk of PCA is **18.3%** for the average U.S. man (from age 40 to 79).

**RECOMMENDATION:**

It is recommended that these results be conveyed to the patient by a qualified provider, including a discussion of follow-up options that are appropriate based on the overall clinical status.
Supplemental Figure II-2. Risk Given to Participants is positively related to Risk Recall.

Supplemental Figure II-2a. Linear relationship of Given Risk with Risk Recall Immediately Following Results Disclosure ($\beta=93.5$, s.e.-1.55, $t=60.2$, $p<0.0001$).

Each plotted circle represents the risk recall for one subject. The trend line, 95% confidence limits, and 95% prediction limits were generated by SAS software.
Supplemental Figure II-2b. Linear relationship of Given Risk with Risk Recall 3 Months Following Results Disclosure ($\beta=94.7$, s.e.=$2.93$, t=$32.4$, $p<0.0001$).

Each plotted circle represents the risk recall for one subject. The trend line, 95% confidence limits, and 95% prediction limits were generated by SAS software.
Supplemental Figure II-3. Risk given to participants is positive and linearly related to post-result anxiety among participants who received risk feedback based on genetic risk score information ($\beta=10.6$, s.e.$=1.77$, $t=5.97$, $p<0.0001$).

Each plotted circle represents the post-result anxiety score for one subject. The trend line, 95% confidence limits, and 95% prediction limits were generated by SAS software.
Supplemental Figure II-4. Text of Study Resource Card, as given to all study participants during study visit 2.

PROSTATE CANCER STUDY RESOURCE CARD

If you would like more information, talk to your primary care physician or urologist about:

1. Your risk assessment
2. The benefits and limitations of prostate cancer screening
3. The pros and cons of potentially risk-reducing medications

If you have a strong family history of prostate and/or other cancers you may wish to discuss this further with a genetic counselor.

To find an urologist, visit: http://www.urologyhealth.org/find_urologist/html/index.asp

To find a genetic counselor, visit:
http://www.nsgc.org/FindaGeneticCounselor/tabid/64/Default.aspx

Or: http://www.magcinc.org/
Supplemental Figure II-5. Prostate Screening Brochure from Centers for Disease Control, as given to all study participants during study visit 2.
### Supplemental Table II-1. Comparison of behavioral outcomes between groups.

<table>
<thead>
<tr>
<th>Analytic group</th>
<th>Participants*</th>
<th>N†</th>
<th>Percent (95%CI)</th>
<th>P (between groups)‡</th>
<th>N†</th>
<th>Percent (95%CI)</th>
<th>P (between groups)‡</th>
<th>N†</th>
<th>Percent (95%CI)</th>
<th>P (between groups)‡</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>All</td>
<td>111/681</td>
<td>16.3 (13.5-19.1)</td>
<td>22/677</td>
<td>3.2 (19.1-45.9)</td>
<td>160/492</td>
<td>32.5 (28.4-36.7)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Randomization Group</td>
<td></td>
<td>GRS-number</td>
<td>34/171</td>
<td>19.9 (13.8-25.9)</td>
<td>8/172</td>
<td>4.7 (1.5-7.8)</td>
<td>45/125</td>
<td>36.0 (27.5-44.5)</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>GRS-pictograph</td>
<td>30/167</td>
<td>18.0 (12.1-23.8)</td>
<td>7/164</td>
<td>4.2 (1.1-7.4)</td>
<td>46/134</td>
<td>34.3 (26.2-42.5)</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>FH-number</td>
<td>25/173</td>
<td>14.5 (9.2-19.7)</td>
<td>4/172</td>
<td>2.3 (0.4-6.6)</td>
<td>29/115</td>
<td>25.2 (17.1-33.3)</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>FH-pictograph</td>
<td>22/170</td>
<td>12.9 (7.8-18)</td>
<td>3/169</td>
<td>1.8 (0-3.8)</td>
<td>40/118</td>
<td>33.9 (25.2-42.5)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Feedback type</td>
<td>GRS</td>
<td>64/338</td>
<td>18.9 (14.7-23.1)</td>
<td>0.065</td>
<td>15/336</td>
<td>4.5 (2.2-6.7)</td>
<td>0.077</td>
<td>91/259</td>
<td>35.1 (29.3-41)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>FH</td>
<td>47/343</td>
<td>13.7 (10-17.4)</td>
<td>7/341</td>
<td>2.1 (0.5-3.6)</td>
<td>69/233</td>
<td>29.6 (23.7-35.5)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Feedback format</td>
<td>NM</td>
<td>59/344</td>
<td>17.2 (13.1-21.2)</td>
<td>0.54</td>
<td>12/344</td>
<td>3.5 (1.5-5.4)</td>
<td>0.72</td>
<td>74/240</td>
<td>30.8 (24.9-36.7)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>PC</td>
<td>52/337</td>
<td>15.4 (11.6-19.3)</td>
<td>10/333</td>
<td>3.0 (1.2-4.8)</td>
<td>86/252</td>
<td>34.1 (28.2-40)</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

* GRS=genetic risk score; FH=family history risk; NM=number format; PC=pictograph format
† Differences of N amongst groups are due to missing data
‡ chi-square tests
§ Based on phone survey
¶ Based on medical records review
Supplemental Table II-2. Relationship between given risk and behavioral outcomes within each randomization group.

<table>
<thead>
<tr>
<th>Randomization Group</th>
<th>Talked to doctor about PSA by 3 months‡</th>
<th>Had PSA by 3 months‡</th>
<th>Had PSA by 3 years§</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>did (N)</td>
<td>Average Given risk (%)</td>
<td>did not (N)</td>
</tr>
<tr>
<td>GRS-number 34</td>
<td>34</td>
<td>137</td>
<td></td>
</tr>
<tr>
<td>GRS-pictograph 30</td>
<td>30</td>
<td>137</td>
<td></td>
</tr>
<tr>
<td>FH-number 25</td>
<td>25</td>
<td>148</td>
<td></td>
</tr>
<tr>
<td>FH-pictograph 22</td>
<td>22</td>
<td>148</td>
<td></td>
</tr>
</tbody>
</table>

* GRS=genetic risk score; FH=family history risk
† Logistic regression
‡ Based on phone survey
§ Based on medical records review
### Supplemental Table II-3. Average anxiety pre- and post-results

<table>
<thead>
<tr>
<th>Analytic grouping</th>
<th>Participants(^a)</th>
<th>(N(^b)</th>
<th>Baseline (S.D.)</th>
<th>Pre (S.D.)</th>
<th>Post (S.D.)</th>
<th>Pre-post Difference</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>All</strong></td>
<td>692</td>
<td></td>
<td>15.01 (4.22)</td>
<td>15.66 (4.20)</td>
<td>15.31 (4.52)</td>
<td>0.0007</td>
</tr>
<tr>
<td><strong>Randomization Group</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>GRSS-number</td>
<td>175</td>
<td></td>
<td>14.91 (4.91)</td>
<td>15.34 (3.93)</td>
<td>15.25 (4.43)</td>
<td>0.4744</td>
</tr>
<tr>
<td>GRSS-pictograph</td>
<td>172</td>
<td></td>
<td>15.83 (4.75)</td>
<td>16.09 (4.49)</td>
<td>15.95 (5.19)</td>
<td>0.1642</td>
</tr>
<tr>
<td><strong>FH-number</strong></td>
<td>174</td>
<td></td>
<td>14.77 (4.16)</td>
<td>15.70 (4.16)</td>
<td>14.92 (4.40)</td>
<td>0.0010</td>
</tr>
<tr>
<td><strong>FH-pictograph</strong></td>
<td>171</td>
<td></td>
<td>14.52 (3.69)</td>
<td>15.50 (4.20)</td>
<td>15.12 (3.93)</td>
<td>0.1478</td>
</tr>
<tr>
<td><strong>Feedback type</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>GRS</td>
<td>347</td>
<td></td>
<td>15.37 (4.47)</td>
<td>15.71 (4.23)</td>
<td>15.60 (4.83)</td>
<td>0.1401</td>
</tr>
<tr>
<td>FH</td>
<td>345</td>
<td></td>
<td>14.64 (3.93)</td>
<td>15.60 (4.18)</td>
<td>15.02 (4.17)</td>
<td>0.0008</td>
</tr>
<tr>
<td><strong>Feedback format</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>NM</td>
<td>349</td>
<td></td>
<td>14.84 (4.14)</td>
<td>15.52 (4.04)</td>
<td>15.09 (4.41)</td>
<td>0.0063</td>
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<tr>
<td>PC</td>
<td>343</td>
<td></td>
<td>15.18 (4.30)</td>
<td>15.80 (4.36)</td>
<td>15.53 (4.62)</td>
<td>0.0393</td>
</tr>
</tbody>
</table>

\(^a\) GRS=genetic risk score; FH=family history risk; NM=number format; PC=pictograph format
\(^b\) Differences of N amongst groups are due to missing data
\(^c\) Anxiety was measured by State-Trait Anxiety Inventory
\(^d\) Non-parametric ANOVA (Kruskal Wallis test) was used for between group tests
\(^e\) Wilcoxon signed rank tests were used for pre-post comparisons
CHAPTER III

BARRIERS TO PRIMARY CARE PROVIDER ADOPTION OF CANCER GENOMIC TESTS MAY BE ADDRESSED THROUGH SHORT CONTINUING EDUCATION SESSIONS.

Manuscript under review.

Title. Barriers to primary care provider adoption of cancer genomic tests may be addressed through short continuing education sessions.

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\textsuperscript{^}\textsuperscript{^}Corresponding Author: Jianfeng Xu, 1 Medical Center Blvd, Center for Cancer Genomics, Wake Forest School of Medicine, Winston-Salem, NC 27157, USA, 336-918-6329, jxu@wakehealth.edu

ACKNOWLEDGMENTS.

This work was partially supported by a grant from the National Cancer Institute: 1RC2CA148463-01.
ABSTRACT.

Purpose: Primary care provider (PCP)-targeted continuing medical education (CME) regarding genomic testing is effective at increasing knowledge and confidence. It is not known if short format CME on genetics can address barriers related to limited knowledge, costs, time, and discrimination concerns.

Methods: We evaluated a 15-minute session delivered during a CME conference to improve PCP knowledge and confidence regarding genetics and new genomic testing. Multi-marker genomic testing for prostate cancer was used as an example. We collected pre- and post- surveys from PCPs.

Results: PCPs (N=45) commonly encountered genetics in clinical practice, although baseline confidence in understanding and utilizing genetics was low. PCP confidence increased significantly from pre- to post-CME in many aspects of genetic testing. Confidence explaining genetic test results to patients significantly increased (31% to 62% confident/very confident; p=<0.0001), but there was no change in the likelihood of ordering genetic tests.

Conclusions: Our results suggest several previously identified barriers to PCP adoption of new genetic technologies may be addressed through short CME sessions. Time and patient cost appear to be key barriers to future adoption of new genetic approaches by PCPs.
Key Words: Primary Care Provider; Genomic Testing; Family History; Genetics; Education
INTRODUCTION.

Genetics is already a common aspect of patient care in primary settings, as 65% of surveyed primary care providers (PCP) had counseled patients on genetic issues in the last 6 months [1-3]. In conjunction with the rapid expansion in PCP use of genetics, a number of studies have evaluated PCP knowledge and attitudes toward clinical genetic testing. These studies have revealed concerns regarding limited knowledge of genetics [4], clinical utility of tests [5], a lack of training and experience [1,6], patient anxiety [2], costs [7], time [8], and potential for discrimination [5,7]. A strong majority of PCP’s (73.7%) rate their knowledge as very/somewhat poor concerning genetics [8]. Fortunately, most PCPs want to learn more about this emerging field, with up to 82% expressing the need for more training on when to order these tests, how to counsel patients, interpret results, and maintain privacy [1,8].

The increasing integration of genetics across medical specialties has been supported by continuing medical education (CME) [9]. Randomized trials and pre-post studies have shown that PCP-targeted CME regarding genetics, particularly for Mendelian forms of breast and colon cancer, is highly effective for increasing genetics knowledge, confidence in management, accuracy of referral decisions, and intent to change practice [10-14]. Genetics education is a moving target, with constant rapid changes. The emergence of new multi-marker genomic tests, and now whole genome sequencing, for common diseases increases the potential for use of genetics in a variety of primary clinical settings, but may also pose new challenges for providers [15]. Effective CME in this area could have broad clinical impact.
Most prior studies of genetics CME for PCPs have reported on long-format trainings consisting of several hours to multi-day events [10-15]. The emphasis on long-format CME for genetics is consistent with many publications on the general effectiveness of CME to improve a variety of educational and practice outcomes [16-20]. Very little research has been reported on the impact of short format CME that would assume the audience has a baseline understanding that can be built upon [21-22]. A recent study found that family practitioners answered more questions correctly following short format (15 minute) CME sessions compared to longer-format (1hr) CME sessions (91% vs 85% correct rate, respectively) [21]. This study evaluates the impact of a short educational session within the standard setting of a regional CME conference, on understanding and confidence of PCPs regarding multi-marker genomic testing.

MATERIALS AND METHODS

Overview

Pre- and post-survey data collection and the 15 min educational intervention were designed to fit into a 40-minute conference timeslot. We conducted this study at two continuing education conferences that offered CME credits through the American Medical Association and American Association of Family Practitioners, during 2013 in the southeast U.S. Both conferences are marketed for PCP’s, and PCP’s have been the primary audience each year.
Content

A master's level genetic counselor led the educational content development based on a review of literature on barriers to PCP use of genetics and prior CME efforts on genetics. The educational session covered content areas identified as barriers by previous PCP studies and new information regarding multi-marker genomic testing. A case study integrating a multi-marker genetic risk report for prostate cancer, illustrated key concepts relevant to common diseases. Topics included: chromosomes, genes, genome-wide association studies, Single Nucleotide Polymorphisms (SNPs) and variation, genetic risk score based on cumulative effect of multiple variant SNPs, a case example of prostate cancer risk assessment using genetic risk score, risk assessment by family history versus genetic risk score, assessment of tests using area under the curve (AUC), comparison of AUC when using family history and genetic risk score to assess prostate cancer risk, clinical utility of genetic risk scores, logistics of genomic test ordering, example genetic risk score results from a research study, example genetic risk score result from a commercial source, genetic discrimination and legal protections, impact of genetic results on patient anxiety, and impact of genetic results on patient medical decision making. At several points, the presentation included several clear distinctions between single gene (Mendelian) genetics, versus new multi-marker genomic tests for common disease.

Surveys

Pre- and post-session surveys assessed six domains with 32 questions; demographics and background characteristics, confidence in understanding and utilizing genetics, effectiveness and predicted use of genetic testing, inclusion of genetic testing in clinical
practice and perceived impact on patients, continuing education in genetics, and perceived provision and sufficiency of standard genetic services. Questions and responses are shown in tables 1 and 2. Paper survey packets were numbered to link pre- and post-surveys. The content and structure of survey questions was modeled after two surveys from the National Cancer Institute, the Physician Survey on Cancer Susceptibility Testing (PSCS) [23] and the National Survey of Primary Care Physicians' Recommendations & Practice for Breast, Cervical, Colorectal, & Lung Cancer Screening (NSPCP) [24]. Changes were made to questions based on content needs and feedback from pilot testing.

We conducted extensive pilot testing of the surveys and the educational session. PCPs and other medical staff provided feedback and confirmed an average completion time of less than 15 minutes for both surveys.

Approval
This study was reviewed and approved by institutional review board at Wake Forest School of medicine.

Statistics
Statistical analyses were performed using SAS 9.2. Comparisons of repeated measures, evaluated using Wilcoxon signed-rank tests (S statistic), assessed the pre-post impact of the short-format CME session. In preparation for the primary analyses, descriptive statistics were calculated to identify variables with pre- to post-session changes. Secondary analyses were calculated using Fisher’s Exact Test to evaluate whether pre-
post session changes were associated with group differences (age, gender, year of graduation, provider type, affiliation with a medical school, or use of family history).

RESULTS.

Description of Study Sample
Approximately 150 physicians registered for the two CME conferences, 48 of whom attended the study educational session. We collected completed surveys from 45 PCPs attending our sessions; 93% of whom reported providing primary care for male patients age >40 years (Table I-1). Genetics has been a common feature of their clinical practice during the past two years, as almost all of these PCPs often ascertain cancer family history information, about a third ordered a genetic test, nearly three quarters had a patient ask about genetic testing, and many had a patient bring genetic results to an appointment (Table II-2).
Table III-1. Demographic and background characteristics

<table>
<thead>
<tr>
<th>Question</th>
<th>Response Options</th>
<th>N</th>
</tr>
</thead>
<tbody>
<tr>
<td>Enrolled</td>
<td></td>
<td>45</td>
</tr>
<tr>
<td>Gender</td>
<td>Male</td>
<td>23 (51%)</td>
</tr>
<tr>
<td></td>
<td>Female</td>
<td>20 (44%)</td>
</tr>
<tr>
<td></td>
<td>Not Reported</td>
<td>2 (4%)</td>
</tr>
<tr>
<td>Age</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>31-40</td>
<td>6 (13%)</td>
</tr>
<tr>
<td></td>
<td>41-50</td>
<td>10 (22%)</td>
</tr>
<tr>
<td></td>
<td>51-60</td>
<td>13 (29%)</td>
</tr>
<tr>
<td></td>
<td>&gt;60</td>
<td>16 (36%)</td>
</tr>
<tr>
<td>Graduation Date</td>
<td>Before 1964</td>
<td>1 (2.2%)</td>
</tr>
<tr>
<td></td>
<td>1964-1973</td>
<td>6 (13%)</td>
</tr>
<tr>
<td></td>
<td>1974-1983</td>
<td>13 (29%)</td>
</tr>
<tr>
<td></td>
<td>1984-1993</td>
<td>12 (27%)</td>
</tr>
<tr>
<td></td>
<td>1994-2003</td>
<td>11 (24%)</td>
</tr>
<tr>
<td></td>
<td>2004-2013</td>
<td>2 (4%)</td>
</tr>
<tr>
<td>Provider type</td>
<td>Physician</td>
<td>39 (87%)</td>
</tr>
<tr>
<td></td>
<td>Physician Assistant</td>
<td>5 (11%)</td>
</tr>
<tr>
<td></td>
<td>Nurse Practitioner</td>
<td>1 (2%)</td>
</tr>
<tr>
<td>Specialty</td>
<td>Family Medicine</td>
<td>23 (51%)</td>
</tr>
<tr>
<td></td>
<td>Internal Medicine</td>
<td>21 (47%)</td>
</tr>
<tr>
<td></td>
<td>Neurology</td>
<td>1 (2%)</td>
</tr>
<tr>
<td>Affiliation with Medical School</td>
<td>Yes</td>
<td>9 (20%)</td>
</tr>
<tr>
<td></td>
<td>No</td>
<td>36 (80%)</td>
</tr>
<tr>
<td>Provide primary care for male patients &gt;40</td>
<td></td>
<td>38 (93%)</td>
</tr>
</tbody>
</table>

Table III-2. Genetics in clinical practice

<table>
<thead>
<tr>
<th>How frequently do you ask your patients about their family history of cancer</th>
<th>Always</th>
<th>Often</th>
<th>Sometimes</th>
<th>Rarely, never, n/a</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>23 (53%)</td>
<td>17 (40%)</td>
<td>3 (7%)</td>
<td>0</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>In past two years, have you?</th>
<th>Ordered a genetic test</th>
<th>14 (31%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ordered a genetic test for cancer susceptibility</td>
<td>13 (29%)</td>
<td></td>
</tr>
<tr>
<td>Referred a patient for genetic testing</td>
<td>25 (56%)</td>
<td></td>
</tr>
<tr>
<td>Had a patient ask you about genetic testing</td>
<td>31 (71%)</td>
<td></td>
</tr>
<tr>
<td>Had a patient bring genetic test results to an appointment</td>
<td>9 (20%)</td>
<td></td>
</tr>
<tr>
<td>Seen advertising materials for genetic tests</td>
<td>23 (52%)</td>
<td></td>
</tr>
<tr>
<td>Positive response to any of the above exposure questions</td>
<td>37 (82%)</td>
<td></td>
</tr>
</tbody>
</table>
Confidence

At baseline, the majority of PCP’s had low confidence in understanding genetic principles, answering patient’s questions about genetic testing, explaining the results of a genetic test to a patient, and recommending genetic testing; post-session, all of these concerns shifted to the minority, for statistically significant decreases (ps<=0.002) (Table III-3a). Understanding the science behind genetic tests was unchanged, with nearly half expressing low confidence (Table III-3a).

Table III-3. Pre-Post Changes

<table>
<thead>
<tr>
<th>3a. Confidence in understanding and utilizing genetics</th>
<th>A little/not at all confident (%)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>pre</td>
<td>post</td>
</tr>
<tr>
<td>Understanding genetic principles</td>
<td>58</td>
<td>38</td>
</tr>
<tr>
<td>Answering patient’s questions about genetic testing</td>
<td>69</td>
<td>40</td>
</tr>
<tr>
<td>Understanding the science behind a genetic test</td>
<td>47</td>
<td>47</td>
</tr>
<tr>
<td>Explaining the results of a genetic test to a patient</td>
<td>69</td>
<td>38</td>
</tr>
<tr>
<td>Recommending genetic testing</td>
<td>67</td>
<td>33</td>
</tr>
</tbody>
</table>

Effectiveness and Utilization

Almost all initially believed genetic testing to assess susceptibility for inherited cancers is very to somewhat effective, and this number declined significantly (p<0.05) following the session (Table III-3b). There were no significant changes in likelihood to utilize genetic services in the next two years from pre- to post- session with regard to ordering tests and using genetic test results in medical management (Table III-3b). When asked about changing aspects of patient care based on results of genetic testing for cancer susceptibility, a majority endorsed all aspects both before and after the educational
session. The only significant pre-post change was an increase in the % reporting they would change the frequency of screening tests (p<0.05, Table III-3c).

### Table III-3. Pre-Post Changes

<table>
<thead>
<tr>
<th>3b. Effectiveness and predicted use of genetic testing</th>
<th>Very/Somewhat (%)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>How effective do you think genetic testing is in assessing susceptibility for inherited cancers</td>
<td>93</td>
<td>84</td>
</tr>
<tr>
<td>How likely to order a genetic test in next 2 years</td>
<td>45</td>
<td>45</td>
</tr>
<tr>
<td>How likely to order a genetic test for cancer susceptibility next 2 years</td>
<td>45</td>
<td>47</td>
</tr>
<tr>
<td>How likely to order a genetic test for assessing a patient's risk for prostate cancer next 2 years</td>
<td>27</td>
<td>36</td>
</tr>
<tr>
<td>How likely to take a patient's genetic test results into consideration when formulating your medical management plan (e.g. when to refer for screening tests, when to refer to a specialist, etc.)</td>
<td>73</td>
<td>70</td>
</tr>
<tr>
<td>Do you believe that you have time in your practice to explain a genetic test and results to patients</td>
<td>34</td>
<td>43</td>
</tr>
<tr>
<td>Do you believe that a majority of your patients will be willing to pay for a genetic test</td>
<td>14</td>
<td>16</td>
</tr>
</tbody>
</table>

### Logistics

Questions about test logistics had large pre- to post-session changes, as less than a third knew where to order a test, refer patients, and identify candidates for testing at baseline; following the education session, all of these percentages shifted significantly toward the positive side (ps<0.005) (Table III-3c). There was a non-significant increase after the intervention in endorsement of having time to explain genetic testing results to a patient. A majority (60%) of PCP’s initially believed patient distress would increase from the results of a genetic test, but this decreased significantly to 27% following the session (p=0.0007, Table III-3c).
### Table III-3. Pre-Post Changes

<table>
<thead>
<tr>
<th>3c. Inclusion of genetic testing in clinical practice and impact on patients</th>
<th>Yes (%)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>pre</td>
<td>post</td>
</tr>
<tr>
<td><strong>Which aspects of patient care would you consider changing based on results of genetic testing for cancer susceptibility</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>a. Frequency of screening tests offered</td>
<td>69</td>
<td>81</td>
</tr>
<tr>
<td>b. Age of first screening test</td>
<td>76</td>
<td>84</td>
</tr>
<tr>
<td>c. Referral to a genetic counselor or specialist</td>
<td>76</td>
<td>84</td>
</tr>
<tr>
<td>d. Frequency of follow up appointments scheduled</td>
<td>63</td>
<td>74</td>
</tr>
<tr>
<td><strong>Do you know where you can order a genetic test for prostate cancer risk</strong></td>
<td>14</td>
<td>67</td>
</tr>
<tr>
<td><strong>Do you know where you can refer patients for genetic counseling regarding a genetic test for prostate cancer risk</strong></td>
<td>32</td>
<td>60</td>
</tr>
<tr>
<td><strong>Can you identify patients who are candidates for prostate cancer susceptibility genetic testing</strong></td>
<td>14</td>
<td>51</td>
</tr>
<tr>
<td><strong>Would you advise a patient against genetic testing based on concern about genetic discrimination</strong></td>
<td>13</td>
<td>4</td>
</tr>
<tr>
<td><strong>Do you believe a majority of your patients would decline genetic testing based on concerns about genetic discrimination</strong></td>
<td>16</td>
<td>16</td>
</tr>
<tr>
<td><strong>Do you believe that results of a genetic test would increase patient distress</strong></td>
<td>60</td>
<td>27</td>
</tr>
<tr>
<td><strong>Do you believe that you have time in your practice to explain a genetic test and results to patients</strong></td>
<td>34</td>
<td>43</td>
</tr>
<tr>
<td><strong>Do you believe that a majority of your patients will be willing to pay for a genetic test</strong></td>
<td>14</td>
<td>16</td>
</tr>
</tbody>
</table>

**Opinions on Education and Implementation**

A strong majority of PCPs felt they should continue to learn about new advances in genetics and would be interested in receiving CME credit on this topic when applied to cancer, and this did not change with CME (Table III-3d). Similarly, only about a third of PCPs thought genetic testing for cancer susceptibility should be provided by specialists rather than PCPs, with no changes from pre- to post-session (Table III-3e). The percent endorsing that family history is sufficient to inform a PCP about inherited risk for cancer fell significantly for prostate cancer (27% to 17%, p<0.05), but not for general cancer risk (Table III-3e).
Table III-3. Pre-Post Changes

<table>
<thead>
<tr>
<th>3d. Continuing education in genetics</th>
<th>Very/Somewhat (%)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>How interested would you be in receiving CME for training in genetic risk assessment and testing for cancer susceptibility</td>
<td>62</td>
<td>65</td>
</tr>
<tr>
<td>How important is it for you to learn about new advances in genetics</td>
<td>84</td>
<td>84</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>3e. Provision and sufficiency of standard genetic services</th>
<th>Strongly agree/agree (%)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Genetic test for cancer susceptibility should be provided by a specialist, rather than by the primary care provider.</td>
<td>31</td>
<td>33</td>
</tr>
<tr>
<td>A patient's family history is sufficient to inform me about inherited cancer risk</td>
<td>34</td>
<td>20</td>
</tr>
<tr>
<td>A patient's family history is sufficient to inform me about his inherited risk for developing prostate cancer.</td>
<td>27</td>
<td>17</td>
</tr>
</tbody>
</table>

Group differences

Secondary analyses found almost no evidence that group differences (age, gender, year of graduation, provider type, affiliation with a medical school, or use of family history) were associated with pre-post session changes. Interestingly, PCP’s that reported less exposure to genetics during the past two years (i.e. had not ordered a test, made referral, had patient ask about, had patient bring results, seen advertising materials on genetics), had greater increases in confidence answering patient questions about genetic testing (p<0.05), compared to those with less exposure. Further inspection of the data showed that these “low-exposure” PCPs also had lower baseline confidence levels answering patient questions about genetic testing, and this difference was significant (p<0.005) compared to “high exposure” PCPs; however, post-session confidence was not significantly associated with the reported baseline exposure to genetics during the past two years.
DISCUSSION.

This study found that a short (15 min) in-person CME intervention delivered in the conference setting produced significant increases in PCPs knowledge and confidence in delivering genetic services to patients. Following the educational session, we observed changes in three of the four most common barriers to genetics in primary care identified by a recent systematic review, including 1) a lack of knowledge about genetics and genetic risk assessment; 2) concern for patient anxiety; and 3) lack of access to genetics [5]. The subset of “low-exposure” PCPs started at a lower baseline confidence and therefore had greater potential for significant increases in their post-session confidence, reaching the same post-session confidence as “high exposure” PCPs. The fourth common barrier, perception of lack of time, was not altered by the session. Although there was a 9% increase in the number of PCP’s that felt they would have time to explain the results to a patient following the education session, this increase was not statistically significant, and a majority still felt they would not have enough time to explain such results. The session included an example risk report from a research study, and the presentation script stated those results were conveyed to patients within a 15-minute appointment; apparently this time was perceived as being too long for PCP’s, and additional studies might wish to explore acceptable appointment time limits for PCP’s to spend explaining genetics results to patients.

We observed mixed findings for a variety of additional barriers that relate to the four common barriers described above. These additional barriers include test cost, concerns regarding genetic discrimination, and confidence in the utility of risk assessment using
either family history or genetic risk score. On test cost, most PCP’s did not believe their patients would be willing to pay for a genetic test, and there was very little change following the education session. Our educational session indicated that the current cost for some services can be as low as $99, and will include risk estimation for many conditions in a single assay. Since these PCP’s felt this price point is too high for a majority of their patients, it would be interesting to further explore the topic of test cost in future studies, particularly if there is downward pressure on test costs. On genetic discrimination, significantly fewer PCP’s would advise patients against testing based on concerns for genetic discrimination, which suggests the educational session alleviated this concern by describing protections offered by the Genetic Information Non-Discrimination Act (2008) and the Affordable Care Act (2010). On PCP confidence for risk assessment by family history and genetic risk score, the results were quite mixed. While the overall utility of family history barely changed, we observed significantly decreased confidence in family history estimation of hereditary prostate cancer risk. This result is consistent with the content of the session, which included discussion of the Area Under the Curve (AUC) for PCa risk assessment by family history, and did not describe such metrics for family history in general. Similarly, application of AUC information may also explain the significant decrease in confidence for genetic testing to estimate hereditary cancer risk. Together, these results provide further evidence that our study participants were able to quickly parse and evaluate details of the presentation.

A key finding was the lack of significant change in PCP expected future use of genetics. We observed little pre- to post-session movement in future intent to utilize genetic information to alter patient care, and no change in predicted ordering of genetic tests in
the next two years. Although few significant changes were observed amongst this subset of measures, we did observe positive increases following the CME session; it is possible that a larger sample size would provide more power to evaluate the moderate differences observed. On the other hand, the general lack of significant differences may provide an overall estimation of the realities facing PCP’s. Although the educational session was able to significantly reduce most of the concerns that have been previously expressed by PCP’s, the inability to strongly address their concerns of time and cost may pose insurmountable barriers for change in practice among this group. We believe these barriers, time and cost, should be central to future efforts to integrate emerging genetic technologies in primary care.

We did not observe changes in PCPs reported understanding of the science behind genetic tests, and this was the only survey item that was not directly addressed in the presentation. This content exclusion was by design, as the 15-minute educational format required that we focus on only the most essential content, and omitted some background content on the science behind genetic tests. We embraced the concept put forth by Feero and Green, that PCPs don’t need to become geneticists to utilize advances in genetics [15]. By aligning educational efforts with the needs and priorities of primary providers, we will likely have a greater impact on their continuing genetics education and clinical practice [15].

While our study did not directly compare short format versus long format CME, our study adds to the emerging evidence in support of the positive impact of short format CME [21-22]. We set out to activate and build upon basic genetics knowledge that is taught at all levels of education leading up to and through medical school. Other types of
emerging technologies may or may not be well suited to short format CME, dependent on whether there is already some integration of basic information in the medical education pipeline that can be used as a foundation. Although we observed significant pre-post changes across a group of PCPs, we also observed variation within the study population that suggested the session had variable impact on individuals. Accordingly, the educational approach that is optimal for most PCPs might not be optimal for every PCP. Future studies may evaluate whether there are differences in the type of content or specific audiences most suitable for short versus long format sessions, and even alternative methods such as online and in-clinic.

We recognize that our study has several strengths and weaknesses. The sample size of only 45 PCPs may be considered small, but was balanced by use of a pre-post design. It is also possible that conference attendees might not accurately represent the general population of PCP’s. While this is a potential issue in terms of generalizing our observational findings, our results showing the positive impact of a short educational intervention should be transferrable to many other CME settings. Third, we were not able to evaluate the extent to which the intervention may change PCPs clinical practices over time; different study designs might be needed for such an evaluation. As a strength, the demographics of our study sample compare favorably with those of U.S. physicians. A report based on the 2013 American Medical Association (AMA) Physician Masterfile (n=1,096,347, all U.S. Physicians excluding medical students), indicates an age distribution that is similar to the age distribution of participating physicians in the current report [25]; however, our study population contained modestly increased percentages of subjects in the 50+ age categories (22% vs 29%). Our study included a higher percentage
of female participants when compared with the AMA Masterfile (51 vs 69% male). A second strength is the alignment between previously identified potential primary care barriers and objectives for the educational session [1-8]. We also believe this intervention has strong dissemination potential; many genetic professionals should be able to convey similar information to primary care providers using a similar format.

Overall, PCPs reported greater confidence in educational, logistical, and ethical aspects of genetic testing for prostate cancer risk after completing the education session, suggesting many of the previously identified barriers can be addressed through short educational sessions. However, careful examination of cost and time barriers will be critical to future studies of genomic practice changes. Our findings also suggest most PCPs already have a working background of genetics, and that a short educational session can activate and build upon existing knowledge and alter opinions by providing supplemental information on new developments in the field. Future studies should evaluate longer term outcomes of these initial changes, including changes in clinical practice. Progress in this area of educational research is critical to ensuring continued implementation of genetics in primary care practice, thus helping ensure maximum health benefit is derived from significant investments made in basic and applied research.
REFERENCES.


CHAPTER IV
SUMMARY AND CONCLUSIONS

The projects that make up this thesis were built around a unifying question: Can genomic test results safely and effectively target healthcare decisions for patients and physicians?

For patients, our findings were remarkable and somewhat surprising. We placed genomic test results for PCa risk in the hands of study participants (i.e. at-risk men), and empowered them to make decisions regarding later PSA screening. We observed that participants used those results to guide (i.e. target) their subsequent cancer screening. We believe this is the first such report showing targeted screening based on multi-marker genomic testing results. Follow-up studies in other populations and with other diseases will be needed to evaluate the universality of these results. However, our results are consistent with studies of high-penetrance genes, BRCA1 and HNPCC, that reported targeting of mammography and colonoscopy, respectively; as patients received higher-risk results, they were significantly more likely to engage in related cancer screenings [1,2,3]. This suggests that risk level serves as a common motivation that drives uptake of various cancer screenings. Based on the strong effects we observed, it will be important for clinical applications to provide precise and accurate genomic risk assessment, because risk levels matter.

On the other hand, we are aware that our findings contrast those from prior multi-marker genetic risk assessment studies, one of which included a variety of potential disease risks while the other focused on colorectal cancer [4,5]. Those prior studies did have
significant differences from ours. The randomized trial of genetic and environmental risk assessment for colorectal cancer utilized subjects that were already non-compliant with screening, and they reported risk results as “average” or “elevated” [5]. Given our major finding, that level of risk given to the patient made a significant impact on subsequent screening uptake, the different results between the two studies is not surprising. The other prior multi-marker study focused on primary outcomes of dietary and lifestyle change in their evaluation of a direct-to-consumer genomic testing situation [4]. That study had several major differences versus our study design; risk results were delivered online, there was no assessment for whether subjects had engaged in disease screenings prior to study enrollment, and the design led to the enrollment of a unique population that had sought out direct-to-consumer testing prior to being invited to participate in the study. Again, it is not surprising that our key findings differed from those multi-marker studies. Yet, there was one consistent finding in each of these studies of multi-marker testing, and in most studies of single gene testing to date; the receipt of testing results tends to result in a reduction of overall anxiety, and there is little evidence of major concerns for patient well-being [4,5].

For physicians, we took an indirect approach to the question of whether genomic test results can safely and effectively target healthcare decisions. Our literature review found many surveys in which PCPs expressed significant doubts about their ability to utilize genetic testing information. Therefore, we sought to test an approach to improve PCP preparedness to use this new information in the clinical setting. Following a 15-minute educational session, confidence explaining genetic test results to patients significantly
increased, and a majority would change aspects of patient care. This project is important because it shows that several specific barriers to use of genetics in primary care can be addressed rather quickly. While time and cost remain a concern, with the availability of direct-to-consumer testing paired with downward pressure on prices, patients may have greater opportunity to order the test on their own, thus reducing these time and cost barriers; however, PCP’s would need to be adequately prepared for patients that bring such results to clinic visits. Similar to prior studies, we found that genetics is already common in PCP clinics, further underscoring the importance of CME for PCPs on emerging technologies such as genomics.

Just as important as “what” we did, is “why” we undertook the projects described herein. Overall, this thesis focused on T3 stage translational research, which examines the practical issues impacting clinical usage, thus seeking to maximize the utility that is established by T2 research [6]. This thesis did not aim to assess the effectiveness of the genomic markers for risk prediction in patients, which would be T2 stage research. As described in the introduction, by the time our RCT began, a number of publications had already established a relatively solid case for the accuracy, precision, and discriminative power of the risk variants included in our multi-marker SNP panel; that evidence continues to mount. In an effort to push forward to the next step of translational research, T3, we chose to apply this new method of risk assessment in a pre-clinical study of patients. Likewise, for PCP’s, we focused on T3 stage research. Rather than run yet another survey of PCPs knowledge and attitudes, and rather than rush into a primary care clinic-based intervention, we took the next step of establishing which PCP barriers could
or could not be addressed through a short CME session. Altogether, the rationale and design for both of these projects was built on prior studies that constituted T1, T2 and early T3 stage research.

Consistent with the translational nature of this thesis, the results reported herein have clear relevance for an issue of direct clinical importance, PSA screening for PCa. Hundreds of thousands of unnecessary biopsies and tens of thousands of treatments occur as a result of PSA screening, and these procedures represent serious concerns. The results of this thesis, that multi-marker testing of GWAS SNPs can be used to stratify risk and motivate targeted PSA screening, compliment recent publications that have suggested that genomic targeting of PSA screening to men at highest risk may reduce overdetection and mortality.

The findings reported in this thesis show that men will utilize the risk information to guide their own decision-making process for PSA screening, with men at highest risk opting to pursue PSA screening much more frequently than those given lower risks. While in some ways our finding may seem like “common sense,” as noted above, prior genomic interventions have failed to show an impact on behavior. Furthermore, cancer prevention studies on topics as diverse as smoking cessation and dietary changes have often failed to observe resulting changes in behavior. While there could be significant differences for each disease (e.g. cancer versus heart disease versus diabetes may all have different motivational thresholds) and for each type of behavioral objective (e.g. dietary and smoking behaviors are notoriously difficult to modify) the results reported in this
thesis suggest that provision of personalized genomic risk information directly to at-risk individuals can motivate behavior changes. The potential to do so, is quite encouraging for future efforts.

A “big picture” question is whether there is anything unique and enduring about the results for the specific application described herein, using risk alleles of GWAS SNPs to assess risk? The GWAS approach truly provided a surge forward in the ability to find genetic associations with complex phenotypes. It should be mentioned that the GWAS targets mostly common genetic variants, with minor allele frequency (MAF) ≥ 0.05. As the ongoing 1000 Genome project (http://www.1000genomes.org/) has revealed, there are many rare genetic variants (MAF < 0.05) that have been or are being discovered. These rare variants are usually not included in conventional GWAS but nonetheless bear the potential to influence complex diseases such as PCa in a non-trivial way. With the decreasing costs associated with next-generation sequencing technologies and Exome SNP arrays, it is expected that additional rare genetic polymorphisms will be identified and studied for their association with PCa. Beyond next generation sequencing of exomes and genomes, there are innovations that allow for the study of epigenetics, proteomics, cell-free circulating DNA, and single cell molecular methods. There are germline and somatic applications for most of those methods. Findings from all such studies have great potential for clinical impact on PCa and other common diseases. As the findings with greatest potential for clinical impact emerge from those studies, translational research similar to what is reported in this thesis should be considered as a tool to develop clinical applications from those discoveries. Therefore, regardless of the
specific application we evaluated, the findings of this thesis have a certain degree of permanence for future clinical translation of basic discoveries.
REFERENCES


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BIRTH: August, 1973
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EDUCATION:

08/09 – Present  PhD Candidate, Molecular Genetics and Genomics Program, Wake Forest University School of Medicine, NC.
08/98 - 05/00  MS Genetic Counseling Program, University of South Carolina School of Medicine, Columbia, SC.
08/92 - 05/96  BS Biology, University of North Carolina at Greensboro, Greensboro, NC.
09/95 – 12/95  Foreign Travel Student, Semester at Sea Program, University of Pittsburgh.
STAFF POSITIONS:

09/13 - present  Proposal Development Officer

Office of Sponsored Programs
University of North Carolina at Greensboro
Greensboro, North Carolina

I am primarily responsible for developing and submitting large multi-disciplinary and multi-center collaborative grant proposals to a wide range of funding agencies and organizations. This includes tracking ongoing funding opportunities, providing writing and editing support, and overall coordination of complex proposals for submission. I also develop and implement new Office of Sponsored Programs (OSP) workshops. I serve all departments, centers, schools and community organizations at UNCG.

06/00 - 08/13  Genetic Counselor / Research Assistant

Center for Human Genomics
Wake Forest University School of Medicine
Winston-Salem, North Carolina

I managed the complete life cycle of genetic research projects. This included concept generation, identification of funding opportunities, grant proposal preparation, budget development, grant submission, post award documentation, study start-up, regulatory approvals, hiring study staff, training study staff, project management, data management, sample management, laboratory coordination, clinic coordination, data analysis, results interpretation, figure preparation, manuscript writing, manuscript submission, and submission of final reports to funding agencies. Additional responsibilities included regulatory oversight (IRB and HIPAA) for a large center, teaching, project mentorship, community workshops, and media relations.

07/96 - 08/98  Laboratory Technician II

Department of Comparative Medicine
Wake Forest University School of Medicine
Winston-Salem, North Carolina

In this prior position, I started up a new molecular biology laboratory as an addition to an existing research team. I was responsible for developing and implementing molecular assays to detect and quantify parvovirus B19 within a variety of sample types. This position involved researching the
existing literature, development and extensive testing of new lab protocols, ordering supplies and equipment, documentation of labwork, production of publication quality images, and written summaries of experimental methods. Techniques primarily consisted of phlebotomy, preparation of samples, DNA extraction, DNA quality control, PCR, nested PCR, gel electrophoresis, radio-labeling, fluorescent-labeling, southern blotting, dot blotting, film processing, and phosphorimaging. I also participated in the daily care of non-human primates, performed phlebotomy, and assisted with procedures such as amniocentesis.

11/93 - 07/96 Undergraduate Research Assistant

Biology Department
University of North Carolina at Greensboro
Greensboro NC

Assisted with a project to localize a gene. Learned and utilized techniques including DNA extraction, gel electrophoresis, PCR, Southern Blotting, Radiolabeling, and Plasmid cloning.

HONORS/AWARDS:

1992 Eagle Scout, Boy Scouts of America
1993 Resident Assistant of the Semester, University of North Carolina at Greensboro
1995 President, BBB biology honor society, University of North Carolina at Greensboro
2010 Woodbadge Training, Boy Scouts of America
2012 Coaching Hall of Fame, YMCA of Kernersville.

PUBLIC ADVOCACY AND AWARENESS:

2000 North Carolina Prostate Cancer Awareness Proclamation from Governor Hunt
2001 - 2008 North Carolina Prostate Cancer Awareness Proclamation from Governor Easley
2003        Participant, Prostate Cancer Coalition of North Carolina planning conference
2006        Participant, Prostate Cancer Coalition of North Carolina planning conference

COMMUNITY RELATIONS:

2006 - 2012    Organizer, Community and Student Lab Tours, Center for Human Genomics, Wake Forest University School of Medicine

EDITORIAL TASKS:

2001    Associate Editor, National Society of Genetic Counselors website
2002- 2004    Editor, National Society of Genetic Counselors website (www.nsgc.org)

PROFESSIONAL COMMITTEE ACTIVITIES:

2002    Co-Chair, Meeting of the North Carolina Medical Genetics Association, Wake Forest University School of Medicine, Winston-Salem, NC, April 26.

2003    Co-Chair, National Society of Genetic Counselors Region III Annual Educational Conference, Asheville, NC, March 22.

2002- 2004    Liaison to the Genetic Resources on the Web (GROW), on behalf of the National Society of Genetic Counselors

2004- 2006    Liaison to the National Coalition for Healthcare Professional Education in Genetics (NCHPEG), on behalf of the National Society of Genetic Counselors
2005- 2006  Board Member and Communications Committee Chair, National Society of Genetic Counselors (NSGC)

THESIS COMMITTEE/GRADUATE STUDENTS:

2002  Tamara Adams, BS  
Practicum Supervisor  
The University of North Carolina at Greensboro, Gerontology Program

2002 - 2003  Angela Schwab, MS  
Chair, MS Thesis Committee  
“The Hereditary Nature of Prostate Cancer: What A Patient Needs to Know”  
The University of North Carolina at Greensboro, Genetic Counseling Program

2007 - 2008  Linda Smith, MS  
Chair, MS Thesis Committee  
“How African American Men Share Prostate Cancer Risk with Family Members: A Pilot Study”  
The University of North Carolina at Greensboro, Genetic Counseling Program

2012 - 2013  Elizabeth Watson, RN  
Advisor, MS Thesis Project  
“Caucasian Men’s Awareness of PSA Screening”  
The University of North Carolina at Charlotte, Nurse Practitioner Program

2013  Alison Witkowski, MD  
Advisor, Medical Student Summer Research Project  
“Attitudes of Primary Care Providers Toward Genomic Testing”  
Wake Forest University School of Medicine, MD Program

2013  Elizabeth Crowder, MD  
Advisor, Medical Student Summer Research Project  
“Attitudes of Primary Care Providers Toward Genomic Testing”  
Wake Forest University School of Medicine, MD Program

INVITED TALKS

2000  “Genetic Counseling for Prostate Cancer”. Forsyth County USTOO prostate cancer support group, Forsyth Medical Center, Winston-Salem, NC. October 9.

2002 “Hereditary Prostate Cancer”. Cancer Support Group, Comprehensive Cancer Center, Wake Forest University Baptist Medical Center, Winston-Salem, NC. January 24.

2002 “The Role of a Genetic Counselor in a Research Setting”
The University of North Carolina at Greensboro Genetic Counseling Program
Greensboro, NC

2002 “Hereditary Prostate Cancer”. High Point USTOO prostate cancer support group, High Point Regional Hospital. April 25.

2002 “Hereditary Prostate Cancer”. Hickory USTOO prostate cancer support group, Catawba Valley Memorial Hospital, Hickory, NC. September 12.

2003 “Hereditary Prostate Cancer”. Greenville USTOO prostate cancer support group, Pitt County Memorial Hospital, Greenville, NC. February 11.

2004 “The Role of a Genetic Counselor in a Research Setting” Genetic Counseling Program, University of South Carolina School of Medicine, Columbia, SC.

2005 “Molecular Epidemiology of Prostate Cancer”. Quarterly Meeting of the North Carolina Medical Genetics Association, Wake Forest University School of Medicine, Winston-Salem, NC, April 22.

2006 “The Role of a Genetic Counselor in a Research Setting” Genetic Counseling Program, University of South Carolina School of Medicine, Columbia, SC.
2007  “Genetic Counseling for Prostate Cancer”. Forsyth County USTOO prostate cancer support group, Forsyth Medical Center, Winston-Salem, NC.

2014  “Careers in Genetics”. UNCG Biology Freshman Introductory Course. (M. Schug)

2015  “Careers in Genetics”. UNCG Biology Freshman Introductory Course. (S. Faeth)

2015  “Careers in Genetics”. UNCG Biology Senior Course. (R. Cannon)

PUBLICATIONS

Journal Articles:


**Book Chapters**

