Implementing Family Health History Risk Stratification in Primary Care: Impact of Guideline Criteria on Populations and Resource Demand

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Abstract:

The Genomic Medicine Model aims to facilitate patient engagement, patient/provider education of genomics/personalized medicine, and uptake of risk-stratified evidence-based prevention guidelines using MeTree, a patient-facing family health history (FHH) collection and clinical decision support (CDS) program. Here we report the number of increased risk (above population-level risk) patients identified for breast/ovarian cancer, colon cancer, hereditary syndrome risk, and thrombosis; the prevalence of FHH elements triggering increased-risk status; and the resources needed to manage their risk. *Study design*: hybrid implementation-effectiveness study of adults with upcoming well-visits in 2 primary care practices in Greensboro, NC. *Participants*: 1,184, mean age = 58.8, female = 58% (N = 694), non-white = 20% (N = 215). *Increased Risk*: 44% (N = 523). *Recommendations*: genetic counseling = 26% (N = 308), breast MRI = 0.8% (N = 10), breast chemoprophylaxis = 5% (N = 58), early/frequent colonoscopies = 19% (N = 221), ovarian cancer screening referral = 1% (N = 14), thrombosis testing/counseling = 2.4% (N = 71). *FHH elements*: 8 FHH elements lead to 37.3% of the increased risk categorizations (by frequency): first-degree-relative (FDR) with polyps age ≥60 (7.1%, N = 85), three relatives with Lynch-related cancers (5.4%, N = 65), FDR with polyps age <60 (5.1%, N = 61), three relatives on same side of family with same cancer (4.9%, N = 59), Gail score ≥1.66% (4.9%, N = 58), two relatives with breast cancer (one ≤age 50) (4.1%, N = 49), one relative with breast cancer ≤age 40 (4.1%, N = 48), FDR with colon cancer age ≥60 (1.7%, N = 20). MeTree identifies a high percentage of individuals in the general primary care population needing non-routine risk management/prevention for the selected conditions. Implementing risk-stratification in primary care will likely increase demand for

related-resources, particularly colon screening and GC. Understanding the prevalence of FHH elements helps predict resource needs and may aid in guideline development.

Keywords: health services | risk stratification | family history | primary prevention

Article:

INTRODUCTION

Primary care providers (PCPs) remain on the periphery of genomic medicine despite the fact that some of these advances are highly applicable to primary care. Reasons for this wait and see attitude include the relative dearth of clinical utility evidence; limited genomics knowledge; and slow diffusion of research into practice [Watson et al., 1999]. An excellent example of this is family health history (FHH) based-risk stratification (one component of genomic medicine), which is widely accepted by PCPs but is rarely practiced [Acheson et al.,2000; Gramling et al., 2004].

Integration of genomic medicine into primary care may be facilitated by starting with a model based upon a widely accepted clinical concept with genomic medicine applicability and building upon it. The Genomedical Connection, a collaboration among Duke University, University of North Carolina at Greensboro, and Cone Health adopted this approach when developing the Genomic Medicine Model for primary care (GMM), which uses FHH as a foundation for bringing personalized/genomic medicine into primary care practices. Its goals include encouraging patients to become active partners in their healthcare, promoting education of patients and providers, and improving adherence to risk-stratified preventive care guidelines [Orlando et al., 2013b]. The core of the GMM is a patient-facing web-based FHH collection and clinical decision support (CDS) program, MeTree, and a series of educational materials designed to meet the needs of each stakeholder.

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The initial CDS conditions (breast/ovarian cancer, colon cancer, hereditary cancer syndromes, and thrombosis) were chosen for the strength of the evidence linking FHH to risk level, clinical relevance, and level of acceptance by PCPs. Potential options for building upon the GMM's FHH core include expanding CDS conditions, adding context appropriate pharmacogenomic or genetic testing recommendations and, where the evidence supports it, incorporating genomic risk and/or diagnostic testing.

When evaluating models designed to overcome barriers in clinical practice, like the GMM, it is important to assess implementation and effectiveness outcomes. To this end we have published papers describing the GMM's implementation, MeTree's development and assessment, and its

successful uptake and acceptance by patients and providers [Orlando et al., 2013a, 2013b; Wu et al., 2013]. In this paper we described the impact of the GMM on one component of effectiveness: identification of patients at increased risk and the resources needed to manage their risk.

METHODS

Study Design and Setting

The GMM was implemented in two community-based primary care practices at Cone Health (Greensboro, NC) as part of a real-world hybrid implementation-effectiveness study that collected data on implementation (i.e., user experience, work flow, uptake, etc.) as well as effectiveness [Curran et al., 2012] from October 15, 2009 to April 14, 2012. All adult patients with upcoming well-visit appointments were invited to participate. Exclusion criteria were: being adopted and not speaking English. On the day of their appointment participants came 1 hr early, completed MeTree, and received a copy of 1) their pedigree and 2) a patient report describing their risk for CDS conditions and with talking points for their appointment with their physician. Provider documents (pedigree, tabular-format FHH, and provider report detailing risk level and appropriate recommendations for risk management and preventive care) were attached to the patient's chart prior to the appointment. The full study protocol has been published [Orlando et al., 2011].

MeTree

MeTree is a web-based software program that collects FHH and personal history from patients, calculates risk, and generates risk-stratified, evidence-based risk-management/prevention recommendations for PCPs. It collects FHH on 48 conditions and enough personal information to calculate the Gail Model and BRCAPRO breast cancer risk scores [Gail et al., 1989; Berry et al., 2002]. Decision support is provided for breast/ovarian cancer, colon cancer, hereditary cancer syndrome risk, and thrombosis. A list of possible recommendations for those at increased risk (i.e., non-routine recommendations) and the evidence supporting them are listed in Table I. Emphasis was placed upon the United States Preventive Services Task Force guidelines with which PCPs were most comfortable. For more details, see the published development and assessment paper [Orlando et al., 2013a].

Table I. MeTree's Non-Routine Recommendation Options for its Clinical Decision Support Conditions

Condition	**Physician report action item**
Thrombosis	*Genetic testing for inherited thrombophilia* [Buller et al., 2004]
	Genetic counseling for comprehensive inherited thrombophilia risk assessment and

	management [Buller et al., 2004]
Breast cancer	Breast cancer surveillance via annual breast MRI and mammography [Berry et al., 2002; Saslow et al., 2007]
	Discuss chemoprevention for breast cancer (tamoxifen or raloxifene) [Fisher et al., 1998; Vogel et al., 2006]
	Discuss chemoprevention for breast cancer (tamoxifen) [Fisher et al., 1998]
Ovarian cancer	Refer to gynecologist for discussion of pros and cons of ovarian cancer screening via annual concurrent transvaginal ultrasound (TVUS) and CA-125 testing [Hampel et al., 2004]
Colorectal cancer	Early colorectal cancer surveillance (beginning at age 40) [Levin et al., 2008]
	Early and more frequent colonoscopies (every 5 years beginning at age 40 or 10 years younger than the earliest diagnosis in the family, whichever comes first) [Levin et al., 2008]
Hereditary cancer syndrome	*Genetic counseling* for comprehensive cancer risk assessment and management [Vasen et al., 1999; Hampel et al.,2004; U.S. Preventive Services Task Force, 2005; Berliner et al., 2007; Levin et al., 2008]
	Cancer risk management for Hereditary Breast and Ovarian Cancer syndrome, according to NCCN guidelines [National Comprehensive Cancer Network, 2011]
	Cancer risk management for Hereditary Nonpolyposis Colorectal Cancer (aka, Lynch) syndrome, according to NCCN guidelines [National Comprehensive Cancer Network, 2011]
	Cancer risk management for familial adenomatous polyposis, according to NCCN guidelines [National Comprehensive Cancer Network, 2011]
	Cancer risk management for Li–Fraumeni syndrome, according to NCCN guidelines [National Comprehensive Cancer Network, 2011]
	Cancer risk management for Cowden syndrome, according to NCCN guidelines [National Comprehensive Cancer Network, 2011]
	Cancer risk management for hereditary cancer syndrome, according to published guidelines [National Comprehensive Cancer Network, 2011]
Note that the italicized physician report action items are those that belong to the "Hereditary Risk" group of recommendations and those that are not italicized belong to the "Familial Risk" group of recommendations.	

Statistical Analysis

All data entered into MeTree, and results of risk calculations and CDS recommendations were stored on a secure SQL relational database and analyzed using R statistical software [R Core Team, 2013].

Although MeTree has been assessed for clinical accuracy through by having a genetic counselor's review every pedigree and recommendation report, we wanted to further assess the analytic validity of MeTree for the guidelines it was intended to implement. To do this we coded all FHH risk factors leading to a non-routine recommendation (i.e., recommendations that differ from normal population based screening practices through referrals, use of different technologies (e.g., breast MRI) or more intensive screening [e.g., starting colonoscopy at age 40 rather than 50]) in R software [R Core Team, 2013]. We then searched each pedigree for the presence of each factor and verified that those with it, received the appropriate recommendation, and that those without, did not. This was done for every possible FHH risk factor-recommendation combination. The accuracy of the code was tested using multiple fictitious pedigrees designed to trigger recommendations. To assess the accuracy of MeTree's Gail Model and BRCAPRO calculations a random sample of 20 pedigrees with scores “above” and “below” the guideline recommended cut-offs were manually entered into the publicly available software programs and compared to scores generated by MeTree.

To approximate the potential increase in resource demands created by applying risk stratification and risk-stratified guidelines to unselected primary care populations we evaluated the frequency of non-routine recommendations. Colonoscopy management of adenomatous polyps or inflammatory bowel disease is not considered non-routine in this paper since these practices are well entrenched in clinical practice and are routine disease management strategies. For each participant the number of non-routine recommendations was calculated and for each disease category the number and percent of participants given a non-routine recommendation were calculated. Non-routine recommendations were further subdivided into “hereditary syndrome risk” (received a genetic counseling (GC) recommendation) (indicating participants are at high risk for a hereditary cancer syndrome) and “familial-risk” recommendations (all non-routine recommendations except genetic counseling and genetic testing, indicating participants are above population-level risk but not at high risk for a hereditary cancer syndrome). We make this distinction because of the tremendous difference in absolute risk in the hereditary risk group versus the familial risk group, even though both are above population level risk. This is demonstrated by colon cancer risk in those with genetic mutations for Hereditary Non-Polyposis Colon Cancer (HNPCC) which are associated with a 40–80% lifetime risk of colon cancer (10-fold higher than population risk), as compared to someone with a first degree relative that developed colon cancer at age ≥ 50, who has a 2- to 4-fold higher than population risk [Hendriks et al., 2006; Schoen et al., 2012]. In calculating percentages, patients with the disease under consideration were removed from the numerator and denominator. For example, participants

with breast cancer were not included when calculating the percent of participants receiving a breast MRI recommendation for prevention.

To better understand which FHH risk factors were driving the receipt of recommendations, we calculated the prevalence of each FHH risk factor and then tabulated according to frequency and type of recommendation (hereditary syndrome risk or familial-risk). To evaluate the relationship between patient characteristics and recommendations we performed Pearson's chi-square (two categorical variables), and analysis of variance *F*-test with Fisher's least significant difference (one categorical and one numeric variable). Age, ethnicity, family size, and percent of family with cancer were analyzed using a regression model to evaluate the relationship between them and the receipt of recommendations. Gender, which is significant due to the inclusion of female only cancers, was included only to obtain adjusted values for the other variables. Model selection was performed using a forward-backward stepwise approach that aims to minimize Akaike Information Criterion (AIC), a measure used to compare the relative quality of competing statistical models by maximizing goodness of fit for those with the fewest number of fitting parameters [Akaike, 1974]. Numeric outcomes were modeled using a standard linear regression, and categorical outcomes using logistic linear regression and bootstrapping was used to calculate the 95% confidence intervals for the mean proportion of affected relatives due to the highly skewed nature of the distributions.

Lastly, to explore the differential impact of other existing, well-accepted guidelines we compared the frequency of recommendations generated when applying the National Comprehensive Cancer Network's (NCCN) guidelines for Colorectal Cancer Screening version 2.2012 and Genetic/Familial High-Risk Assessment: Breast and Ovarian version 1.2012 (available athttp://www.nccn.org/professionals/physician_gls/f_guidelines_nojava.asp#detection), and the Michigan Department of Community Health's Cancer Family History Guide (available at http://www.michigan.gov/documents/mdch/PocketToolCard_344670_7.pdf) to the pedigrees collected by MeTree, using the same process as the one described for analytic validity.

RESULTS

Patient Characteristics

The study population and a study flow diagram were previously published [Wu et al., 2013]. A total of 1,184 patients who were similar to the underlying clinic population except for slightly more women (58% vs. 42%) and fewer non-whites (20% vs. 25%) participated. A total of 27,406 relatives were entered into MeTree (see Table II). The median number of relatives entered per pedigree was 21 (range 10–70), the median number of first degree relatives (FDRs) entered was 5, and of second degree relatives (SDRs) was 15. For breast cancer 19% of participants had at least one affected FDR (2% had >1 affected FDR), and 21% had at least one affected SDR (5% had ≥2 affected SDRs, of which 4 had ≥4). Four male relatives were reported to have breast cancer. For colon cancer 11% of participants reported at least one affected FDR (1% had >1

affected FDR) and 16% had at least one affected SDR (4% had >1 affected SDR, of which 2 had >3). There were 12 participants with at least one relative with Hereditary Breast and Ovarian Cancer Syndrome (HBOC) and seven with at least one relative with Hereditary Non-Polyposis Colon Cancer (HNPCC). No participants reported relatives with Familial Adenomatous Polyposis (FAP), Li–Fraumeni Syndrome, or Cowden Syndrome. Table III lists the prevalence of CDS diseases by relative across all participants (e.g., average percent of relatives with breast cancer/pedigree for the study population) as well as for the subgroup of those with at least one relative with the disease under consideration (e.g., average percent of relatives with breast cancer/pedigree for only those participants with a FHH of breast cancer). The familial clustering of CDS diseases is evident by the high disease prevalence among the small proportion of families with at least one relative with the condition, while the predominance of families had no affected relatives. This is in opposition to the more even distribution that occurs when there is no clustering.

Table II. Population Characteristics

	Study patients (N = 1,184), N (%)
Gender	
Male	490 (41.4)
Female	694 (58.6)
Ethnicity	
White	969 (81.8)
Black	159 (13.5)
Other	56 (4.7)
Age	
Mean (SD)	58.8 (11.8)
Education	
HS or less	158 (13.3)
Some college	245 (20.7)
College degree	461 (38.9)
Gail score (SD)	0.0184 (0.01)
No. of relatives (range)	22.89 (8–71)
Disease prevalence (N (%))	
Breast cancer (females only)	45 (6.5%)
Colon cancer	5 (0.4%)
Diabetes	110 (9.3%)
Heart attacks	36 (3.0%)
Thrombosis	53 (4.5%)
Asthma	146 (12.9%)
[a] Adapted from table published in open access journal [Wu et al., 2013]. http://www.biomedcentral.com/1471-2296/14/111.	

Table III. Prevalence of Clinical Decision Support Conditions Among Participants' Relatives

	All participants[a] proportion of relatives affected mean (%) (CI)	**Participants with an affected relative[b] number of participants N (%)**	**Participants with an affected relative[c] proportion of relatives affected mean (%) (CI)**
Breast cancer[d]	5% (4.7%, 5.6%)	441 (37%)	14% (12.9%, 14.5%)
Ovarian cancer[d]	1% (0.9%, 1.3%)	113 (10%)	11% (9.9%, 12.5%)
Colon cancer	1% (1.3%, 1.7%)	279 (24%)	6% (5.92%, 6.76%)
Hereditary cancer syndrome	0% (0.1%, 0.3%)	29 (2%)	8.7% (6.7%, 10.9%)
Thrombosis	2% (1.6%, 2.0%)	324 (27%)	7% (6.1%, 7.0%)

[a] Values reported in the column represent the percent of relatives within each participant's pedigree that have the specific condition—averaged across all participants (N = 1,184).
[b] Values reported in the column represent the number of participants who had at least one relative with the specific condition. This subset represent the pedigrees averaged in the column to the right.
[c] Values reported in the column represent the percent of relatives within each participant's pedigree that have the specific condition—averaged across the participants with an affected relative (column to the left).
[d] The mean percent of affected relatives is calculated using only female relatives as the denominator for these two conditions.

Analytic Validity

MeTree appropriately generated recommendations for all participants based upon the FHH risk factors specified in the guidelines and accurately calculated BRCAPRO [Berry et al., 2002] and Gail Model [Gail et al., 1989] risk scores in the 20 validation cases.

Recommendations

There were 761 non-routine recommendations generated on 44% of participants (523/1,184). Of the 761 recommendations 55% (416/761) were for “hereditary syndrome risk” (genetic counseling recommendation). Among participants receiving a non-routine recommendation 63% (330/523) received a genetic counseling recommendation (22 related to thrombosis, 301 to cancer, 7 to both), and 59% (307/523) received a “familial-risk” recommendation. This includes 176 participants who received more than one recommendation (128 with 2 recommendations and 48 with more than 2). Of the 128 with 2 recommendations, 17 received 2 GC recommendations, 76 received 1 GC and 1 “familial-risk” recommendation, and 35 received 2 “familial-risk” recommendations. Of the 48 with >2 recommendations, 8 received all GC recommendations, 2 received all “familial-risk” recommendations, and the remaining 38 received some combination of GC and “familial-risk” recommendations. When considering resource impact, 330 (28.4%)

needed referral to a GC, 14 (1.2%) a referral to gynecology, 221 (18.6%) more intensive colon cancer screening, and 10 (0.8%) breast MRI. Table IV lists the number and percent of participants receiving "hereditary syndrome risk" and "familial-risk" recommendations across the full study population and within the subgroup of participants eligible for the recommendation (e.g., removing men from the denominator of ovarian cancer recommendations).

Table IV. Frequency of Hereditary Syndrome Risk and Familial-Risk Recommendations for Each Clinical Decision Support Condition

Disease	**Recommendation**	**Frequency among all participants (N = 1,184), N (%)**	**Frequency among eligible participants[a], N (%)**
Hereditary syndrome risk	*Genetic counseling*[b]	308 (26.0%)	308/1,184 (26.0%)
Breast cancer	*Breast MRI*	10 (0.8%)	10/694 (1.4%)
	Chemoprophylaxis	58 (4.9%)	58/694 (8.3%)
Colon cancer	*Start colon screening early*	114 (9.6%)	114/1,178 (9.7%)
	More frequent colonoscopies	107 (9.0%)	107/1,178 (9.1%)
Ovarian cancer	*Referral to gynecology*	14 (1.2%)	14/694 (2.0%)
Thrombosis	*Genetic testing*[b]	42 (3.5%)	42/1,184 (3.5%)
	Genetic counseling[b]	29 (2.4%)	29/1,184 (2.4%)

[a] The number of participants eligible for a recommendation in that disease category. Those with the disease are removed and for breast cancer and ovarian cancer, men are removed.
[b] These recommendations make up the "hereditary syndrome risk" group, the others up the "familial-risk" group.

Prevalence of FHH Risk Factors

To better understand which FHH risk factors were driving the receipt of non-routine recommendations, we calculated the prevalence of each and categorized according to type of recommendation: "hereditary syndrome risk" (genetic counseling referral) or "familial-risk." Data are presented as the number of individuals with the risk factor and its prevalence in the population (N/1,184). Among "hereditary risk" recommendations (N = 416) the most common FHH risk factors were: (1) three or more relatives with HNPCC related cancers (N = 65, 5.4%); (2) three or more relatives on the same side of the family with the same cancer (N = 59, 4.9%); (3) two or more relatives with breast cancer, at least one with an age of onset at or before 50 years (N = 49, 4.1%); and (4) at least one relative with breast cancer at or before 40 years (N = 48, 4.1%). Among "familial-risk" recommendations (N = 345) the most frequent FHH risk factors are: (1) an FDR with colon polyps diagnosed at or after age 60 (N = 85, 7.1%) (start colorectal cancer surveillance at age 40); (2) an FDR with colon polyps diagnosed before age 60

(N = 61, 5.1%) (start colonoscopies at age 40 or 10 years prior to relative's age at diagnosis and perform every 5 years); (3) a 5-year Gail score ≥1.66% (N = 58, 4.9%) (consider breast cancer chemoprevention); and (4) an FDR with colon cancer diagnosed at or after age 60 (N = 20, 1.7%) (start colorectal cancer surveillance at age 40).

Factors Related to Receiving Non-Routine Recommendations

In multivariate analysis the likelihood of receiving any non-routine MeTree recommendation was only significant for mean family size (24.5 for yes recommendation vs. 21.6 for no, $P = 4e{-}8$) and mean percent of family with cancer (17.3 for yes vs. 10.9 for no, $P = 2e{-}26$), while the likelihood of receiving a genetic counseling recommendation was significantly higher for individuals with older age (58.3 for no GC vs. 59.9 for yes, $P = 0.03$), larger mean family size (22.2 for no vs. 24.7 for yes, $P = 8e{-}6$), and mean percent of family with cancer (11.2 for no vs. 20.3 for yes, $P = 6e{-}44$). These findings are not surprising given the dependence of recommendations upon the presence of disease within families. This same trend was also present across disease specific recommendations such as breast MRI.

Comparison to Other Sources

To explore the differential impact of other well-accepted guidelines and screening tools on non-routine recommendation frequency, and thus resource needs, we compared MeTree genetic counseling recommendations (for breast, ovarian, and colon cancer) to those that would have been generated if (1) the *National Comprehensive Cancer Network (NCCN) Guidelines* for breast/ovarian and colorectal cancer screening and (2) the *Michigan Department of Community Health's Cancer Family History Guide* (CFHG) were applied to the same population. Table V reports the frequency of genetic counseling recommendations for each and where they agreed and disagreed.

Table V. Comparison of Genetic Counseling (GC) Referral Recommendations Between MeTree, and the NCCN's Colon and Breast Cancer Guidelines, and the Michigan Department of Community Health's Cancer Family History Guide (CFHG)

	MeTree GC referral		**Total**
	No, N (%)	**Yes, N (%)**	
CFHG GC referral			
No	768 (64.9%)	94 (7.9%)	862 (72.8%)
Yes	86 (7.3%)	236 (19.9%)	322 (27.2%)
Total	854 (72.1%)	330 (27.9%)	1,184 (100%)
NCCN breast cancer GC referral			
No	891 (75.3%)	12 (1.0%)	903 (76.2%)
Yes	114 (9.6%)	167 (14.1%)	281 (23.7%)
Total	1,005 (84.9%)	179 (15.1%)	1,184 (100%)
NCCN colon cancer GC referral			
No	1,070 (90.4%)	103 (8.7%)	1,173 (99.1%)

Yes	0 (0%)	11 (0.9%)	11 (0.9%)
Total	1,070 (90.4%)	114 (9.6%)	1,184 (100%)

The total number of MeTree and CFHG genetic counseling recommendations was similar (330 vs. 322) and agreement was 85% (agreed to refer + agreed not to refer) with a $\kappa = 0.619$. When comparing MeTree to the NCCN hereditary breast/ovarian cancer guidelines, genetic counseling was recommended less frequently by MeTree (179 vs. 281); agreement was 89% with a $\kappa = 0.664$. Most of the difference was due to NCCN referring for either any relative with ovarian cancer (N = 66, 65%), or for a family member with breast cancer onset at or before age 45 (MeTree uses a cut-off of 40) (N = 32, 32%). This pattern was reversed when looking at the NCCN hereditary colon cancer guidelines with MeTree recommending genetic counseling for 114 and NCCN for only 11; agreement was 90% with a $\kappa = 0.162$. This difference was entirely due to MeTree's inclusion of stomach, ovarian, pancreatic, and brain cancers (Bethesda Criteria) as a risk factor for HNPCC, while NCCN included them as a risk factor only for individuals with colon cancer themselves or an FDR or SDR with colon cancer [Umar et al., 2004].

DISCUSSION

Risk stratification and risk-stratified preventive guidelines are a critical component of incorporating genomic and personalized medicine into primary care and are important tools for improving both the quality and the cost-effectiveness of medical care.

Risk stratification and risk-stratified preventive guidelines are a critical component of incorporating genomic and personalized medicine into primary care and are important tools for improving both the quality and the cost-effectiveness of medical care.

When interventions are targeted to risk level, the balance of risk and benefits shift towards applying the right “treatment” to the right patient at the right time [Grimes et al., 2012]. However, risk stratification is time intensive and requires the collection of high quality FHH and personal data that is often not feasible in the context of a routine primary care visit [NIH, 2009]. Risk stratification and clinical decision support tools, like MeTree, Family Healthware™ [Yoon et al., 2009], Health Heritage© [Cohn et al., 2010], Hughes riskApps™ [Ozanne et al., 2009], and others are designed to overcome these obstacles. In this paper we show that when implementing MeTree in an unselected primary care population, 44% of patients meet criteria for non-routine risk-management/prevention strategies for breast/ovarian cancer, colon cancer, hereditary cancer syndrome risk, and thrombosis and that many of the recommendations clustered within participants (176/523 received more than 1 recommendation)—not surprising given the familial clustering of conditions upon which recommendations were based (Table III). This supports the notion that MeTree is able to capture high-risk individuals and appropriately target preventive resources.

The high frequency of non-routine recommendations may mean that successful implementation will result in an unanticipated demand for recommended resources; largely genetic counseling (26% of study population) and colon cancer screening modalities (18.6% of study population) (Table IV). Genetic counseling is an already limited commodity and few PCPs have an established relationship with a genetic counselor or medical geneticist. While increased training in these fields will help, broader adoption of alternative counseling modalities such as telegenetics and phone counseling can expand access and help to accommodate increases in demand [Hemminki et al., 2008; Neale et al., 2013]. For colon cancer screening, PCPs and gastroenterologists may end up sharing the additional workload, depending upon screening modality (in some recommendations colonoscopy is required, but in others any screening modality is acceptable). For example, if in an increased surveillance recommendation, choice of modality is optional (such as when an FDR is diagnosed with polyps at or after age 60), and providers opt for fecal occult blood cards, management would fall to the PCP; alternatively, if colonoscopy is chosen as the modality or specified by the recommendation, increased demand would fall upon gastroenterologists possibly creating a need for more gastroenterologists or for existing gastroenterologists to spend more time performing colonoscopies. Altogether, this suggests that the feasibility of adopting risk-stratification should take into consideration the expected frequency of non-routine recommendations derived from risk-stratification and the potential for higher demand for limited resources.

One way to predict the frequency of non-routine recommendations is to know the prevalence of FHH risk factors in the underlying population. Understanding prevalence would allow policy makers to project resource needs and could guide decision making prior to implementation. In our study, many of the recommendations were due to the high prevalence of a few FHH risk factors. Eight were responsible for 18.5% of genetic counseling and 18.8% of familial-risk recommendations—in total 37.3% of all recommendations. The remainder was responsible for <3% each. Thus even without monitoring all FHH risk factors, awareness of prevalence can help identify selected factors to monitor when estimating changes in resource availability.

The effect that prevalence can have on a population is demonstrated by the difference in MeTree's and NCCN's genetic counseling recommendations for HNPCC risk. Both incorporate the Bethesda criteria in their risk assessment; but in the case of NCCN it was only included when the participant or his/her close relative had colon cancer; therefore, the prevalence of colon cancer limited the application of the Bethesda criteria. This one difference resulted in 10-fold fewer referral recommendations by NCCN (N = 11) than by MeTree (the same 11 plus 103 more). Even when the overall recommendation numbers seem almost identical, such as in the comparison of MeTree (N = 330) to the Cancer Family History Guide (N = 322), differences at the individual level are present. In this case only 236 were referred by both, the other one-third were referred by one but not the other and vice versa. Though the relatively high agreement seems counterintuitive when focusing upon the differences in genetic counseling referral recommendations, the agreement values and the Kappas reflect the high frequency with which

the guidelines agreed not to refer the majority of participants. The lower Kappa for NCCN colon cancer is due to the very low number of “non-routine” recommendations compared to routine, rather than a high disagreement rate. Extrapolating, low prevalence leads to a low impact on the overall population, but still may profoundly affect individuals (identifying small numbers of individuals who would otherwise not have been found to be at high risk); but high prevalence leads to a high impact on both populations and individuals.

These data highlight the importance of understanding FHH risk factors, their prevalence, and their relationship to outcomes in order to inform guideline development. However, in contrast to sensitivity and specificity for which data exists, surprisingly little is known about prevalence in the general population and what is published references selected populations, typically probands affected by a disease of interest [Hemminki et al., 2008; Grimes et al., 2012; Neale et al., 2013]. In addition, guideline development teams rarely, if ever, consider the downstream consequences of implementation. Once prevalence and population impact is clearly understood including downstream impact on resource use should also be considered. One way to create this knowledge-base is to develop and maintain a high quality FHH database comprised of unselected representative U.S. individuals. This effort could be similar to those currently underway for genetic sequencing [Genomes Project et al., 2012].

Limitations of our study are several. First, MeTree's analytic validity could have been poor and thus not appropriately represent the risk-stratified guidelines. While it had undergone several phases of assessment, including a review of all pedigrees and recommendations by a genetic counselor during the first 6 months of the clinical trial [Orlando et al., 2013a], we wanted to systematically assess the programming structure using the entire study population. The results suggest that MeTree is accurate and that widespread adoption of the guidelines upon which it is based would result in a similar frequency of non-routine recommendations (given differences in the underlying populations). Second, the patient population in our study may not have been representative of primary care populations in general or even of the clinics from which they were recruited. In particular it is possible that primary care patients with a strong FHH of cancer would be more aware of their risk or more aware of the diseases present in their family and thus more likely to participate in the study, which would skew the frequency of non-routine recommendations upward. Three points argue against this: participants were demographically quite similar to the clinic population, relative-type recurrence-risk ratios from our population are similar to those reported in other unselected populations (data not reported here but is in review) [Risch, 1990], and the percent of participants identified as at increased risk is consistent with that reported by other primary care based risk-stratification tools, 42–82% depending upon the number of conditions considered and the criteria for assigning risk (FHH risk factors) [O'Neill et al., 2009; Cohn et al., 2010; Rubinstein et al., 2011]. When considering only conditions represented in MeTree's CDS, the Family Healthware Trial categorized 42% as higher than population risk, almost identical to MeTree's 44% [O'Neill et al., 2009]. A third limitation is the dependence of MeTree (and any other tool with the goal to improve uptake of guidelines) upon

the validity of the guidelines. As shown in this paper, small differences in guideline criteria result in big differences in population impact, and many are based on consensus. Making sure that the guidelines are better informed through better data is one of the main objectives of this paper which serves as a call to create more data driven guidelines. In addition, guidelines change and keeping tools, like MeTree updated are critical to their functionality. In our case, we have a team dedicated to updating the algorithms as guidelines change. See the referenced paper for more details on this process [Orlando et al., 2013a]. Finally, the fourth limitation is that in the resource demands discussion we assumed providers and patients would adhere to the CDS recommendations. Since there may be many reasons why participants should not undergo the recommended action, adherence will never be complete. Future research exploring factors affecting adherence to the recommendations will help to improve the accuracy of projections. Taken together these suggest that (1) MeTree performs appropriately and its result are representative of what might be found when implementing risk-stratification in primary care, and (2) given the few conditions represented in MeTree's clinical decision support, broadening risk stratification to incorporate all evidence-based risk-stratified action-oriented risk-management/prevention guidelines would lead to considerably more non-routine recommendations.

In conclusion, MeTree can successfully integrate guideline risk stratification and management into the care of primary care populations but that in the process we should anticipate an increase in demand for certain resources, particularly genetic counseling. Developing a database of personal and FHH is one way to anticipate these demands and help prepare for them as well as to inform guideline development.

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