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GeneHome – a Novel Model to Deliver Care to Individuals with Genetic Predisposition to Cancer

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Abstract

Genetic testing for hereditary cancer predisposition is more widely available, resulting in more patients being identified as carriers of pathogenic variants (PV) of cancer susceptibility genes. PV carriers may be at high risk for multiple cancers of different organ systems. Traditional high-risk cancer screening is often organ specific and conducted separately by specialists. However, with many genes associated with 3 or more types of cancer risks, coordination of such cancer screening can be overwhelming for patients and providers. At Moffitt Cancer Center (MCC), GeneHome clinic functions as a "home" to conduct and co-ordinate prevention, screening, counseling, and education for individuals carrying germline genetic PVs across the entire spectrum of cancer genes. The screening includes, but is not limited to, history review, physical examination, image studies, blood tests, urine tests, and endoscopy. GeneHome is a novel model for genetic high-risk cancer surveillance and has grown in 4 years since establishment. We sought to study various characteristics of the patient population it serves, common themes in referral patterns and evolution of the clinic since its inception. A total of 821 patients were seen over 42 months, encompassing PV carriers of 46 genes. Patients were 84.9% female and 13.3% male. Most PVs were of *BRCA1* and *BRCA2*. Most patients had private insurance, and most were from Florida. Annual increase in patient visits was over 74.7% over the last year. Overall, GeneHome has been well accepted by providers and patients and is a valuable service for patients with a genetic predisposition to cancer.

Keywords

genetic predisposition to cancer, genetic carrier, high risk, screening, surveillance, genehome

Introduction

The number of individuals affected with cancer predisposition syndromes identified by genetic mutations has grown dramatically since 1996.[1] Genetic testing allows these patients and their family members to acquire information regarding their risk for various cancers. Positive test results allow them to be alerted to the high-risk cancer surveillance. Myriad Genetics was the first to introduce clinical cancer susceptibility germline genetic testing by offering *BRCA1/2* analysis. From 1996 through 2013, Myriad held a patent on the *BRCA1/2* genes and maintained the high cost well over $2000 USD for these two genes. In 2013, the U.S. Supreme Court ruled that human genes could not be patented, creating competition and driving down the cost of testing. In 2014, panel genetic testing using next generation sequencing became available, allowing testing of multiple genes simultaneously at an affordable cost. The cost for a panel of 80-100 genes has decreased to $250 USD if paid out-of-pocket. Patient accessibility to cancer genetic testing has improved significantly, along with greater provider awareness, more provider-patient discussion about

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genetic risk for cancer, genetic laboratory marketing campaigns, and direct-to-consumer testing.[2] More people than ever before have completed genetic testing based on personal or family history of cancer and are found to carry genetic variants predisposing to cancer. The workflow after genetic testing encompasses eight areas: (1) For a positive pathogenic variant (PV, or mutation), proper management for cancer risk of various organs based on individual cancer predisposition genes is to be outlined, recommended, and explained to the patient and other health providers. (2) Genetic test result interpretation can be complex. A patient with negative result may still need enhanced cancer screening based on family history. Majority of the time, an equivocal result (variant of uncertain significance - VUS) can be treated as negative result. Occasionally, a VUS is considered highly suspicious for pathogenicity if suggested by molecular features and the individual and family histories. In such situation, the highly suspicious VUS is treated as a PV to ensure proper management can be delivered timely. (3) For PV carriers who are cancer free or who have previous history of cancer, gene specific cancer prevention or enhanced screening need to be carried out. Enhanced cancer screening may need to be initiated early, and to be done more frequently than average people, such as once every 6 months or up to every 5 years. (4) For PV carriers who are undergoing cancer treatment, the oncology providers need to be aware of the newly emerged targeted cancer treatment related to the germline gene PVs. 5) The biological relatives of the carriers are recommended to undergo cascade testing. The PV carriers have to be the advocates for their family. (6) During the course of longitudinal care for a PV carrier, additional genetic testing may be indicated when new personal and family history emerges, or when new genetic testing technology becomes available. A VUS may be reclassified so the care plan needs to be adjusted accordingly. (7) Most of the genetic cancer syndromes are rare that the general health providers may benefit from ongoing communication with genetic specialists to provide proper care to the PV carriers based on updated information and guidelines. (8) PV carriers often need guidance and direct referral to the specialists who can provide the needed high-risk screening. When a cancer is diagnosed, the patient and providers need the guidance and direct referral to the specialists for treatment.

Traditional high-risk cancer surveillance is often organ specific, housed individually and conducted separately by specialists. Ongoing and intensified surveillance required for these patients can often be overwhelming. For patients who carry a genetic PV that predisposes them to various types of cancer, multiple dimensions of care are often necessary, including screening, health maintenance, coordination of screening, diagnosis, treatment, ongoing counseling and education. Genetic counseling assists patients in making informed decisions about their health and treatment, improves knowledge of cancer genetics, modifies cancer risk perceptions, as well as reducing cancer anxiety.[2]

In order to succinctly and cohesively conduct surveillance, counseling, education and coordination of care for patients with genetic PVs, Moffitt Cancer Center (MCC) has implemented the GeneHome (GH) clinic. Instead of focusing on selected organ systems, this clinic provides the patients with a single clinic from which they may have all of their high-risk cancer surveillance completed and monitored. GH is unique and different from traditional genetic counseling services that it offers longitudinal comprehensive care to these high-risk individuals.

The clinic serves as a centralized hub coordinating between genetic counseling, diverse clinical programs within the institution, and various community health care providers. The clinic is staffed by a board-certified medical geneticist and an advanced practice professional with cancer genetic certification and over a decade of experience in genetic counseling. A medical oncologist, a dedicated registered nurse, and a medical clinical assistant were later added to the team in the third year since the establishment. There are 6 certified genetic counselors also housed within the genetics department, but whose duties are distinct and separate from this unique clinical environment.

There are two major groups of patients who are referred to GH to seek high risk cancer screening. One group was recently genetically tested and found to carry a germline PV in a cancer predisposition gene. They are often referred by genetic counselors and other providers who ordered their genetic testing. The other group of patients were previously found to carry the genetic based risk who underwent high risk screening with other providers either inside or outside the institution and are now referred for GH to assume the role of screening. Patients may present with no prior history of cancer, were recently diagnosed with cancer, or are cancer survivors at the time of being identified as a genetic carrier of cancer predisposition.

For each genetic PV carrier, GH provides and coordinates services in all eight areas described above. GH not only coordinate screening for high-risk cancers, but also for cancers that warrant screening based on the general population guidelines. The screening guidelines for both categories are based on National Comprehensive Cancer Network (NCCN) recommendations.[2] Just like a clinical care visit, a GH provider reviews symptoms and medical histories, performs physical examination, orders screening or diagnostic tests, and refers to specialists when needed. In addition, genetic evaluation is also performed. During the initial visit, three generation family history is reviewed, comprehensive genetic counseling and education is provided to all patients regardless of prior history of genetic counseling. Recommendation and direction for biological relatives to undergo cascade genetic testing is given. During return visits, updating genetic variant classification, family history and clinical recommendation are part of the care. The clinical recommendations for screening are coordinated closely with the patients including helping them establish with any referred providers. Laboratory tests, imaging, and endoscopies are mostly ordered by GH providers, some are

ordered by other providers either inside the center or outside the center, depending on the availability, logistics and patient's preference. For example, due to the residing geographic location, a woman may choose to have breast MRI ordered by a GH provider to be performed in the cancer center, mammogram and pap smear by her local gynecologist, and colonoscopy by her local gastroenterologist.

GH has also established direct referral relationships with other disease specific provider groups within the cancer center for further directed examinations, tests or therapies recommendations if a cancer is identified. For many complex patients with identified disease specific risks, the cases are presented in the multidisciplinary disease specific tumor boards within the center, such as the neurofibromatosis tumor board, to help to coordinate their complex care. For patients who are actively on therapy, close collaboration with the primary oncologists occurs as well by direct communication with the treatment teams to ensure proper screening is obtained when it is appropriate and safe.

As our approach with GH is unique in offering a single program with complete coordination of cancer care and surveillance for PV carriers within a comprehensive cancer center, we sought to study various characteristics of the patient population it serves, common themes in referral patterns and evolution of the clinic over 42 months since its inception.

Methods

Over the 42-month period since its establishment, GH providers have compiled information from each patient within a program specific database. Location, referral, visit and payor data was compiled via performance manager decision support. A retrospective analysis was conducted for all patients under surveillance at the MCC GeneHome clinic from 2017-2020. We analyzed the number of new patient visits (patient was self-referred or referred by providers outside the cancer center, therefore GeneHome visit was the first encounter in the center), new established patient visits (patient was previously cared by other services in the center, then self-referred or referred by providers to GH for consultation and/or screening), and established patient visits (patient returns to GH for follow up evaluation and screening). We compared the number of patient visits with the physician vs. the advanced practice provider. We also examined the patterns of referral source, such as referral from providers within the institution (internal referral), from outside providers (external referral) and self-referral. Use of charity care, Medicaid, Medicare and HMP/PPO insurance providers was analyzed. We also explored in-state vs. out of state visits and evaluated the number of patients coming from each Florida county to better gauge the catchment area of the GH. Finally, we assessed the type and frequency of genetic mutations present in our patient population and which primary organ system patients were being treated for.

Results

There was a total of 821 patients seen in GH clinic from 2017-2020. Of these patients, 697 were female (84.9%), 109 were male (13.3%), 1 female to male transgender, and 14 patients not classified. Patient age ranged from 16 to 84, with an average age of 47.6. Total number of patient visits was 1407, with 138 new patient visits who were self-referred or referred by external providers (9.8%), 683 new established patient visits (48.5%) who were self-referred or referred by internal providers, and 586 established patient visits (41.6%). A large number of patients had only a single visit to GH (50%), and of those who had multiple visits a majority had 2-4 follow up visits (90%, range 2-8 visits). Since the establishment of the clinic, new visits increased significantly, with annual increase of 50.5% in the second year and 74.7% in the third year.

There was a diverse referral base identified including primary referral from physicians, advanced practice providers (APP), and Genetic Counselors. The majority of referrals came directly from providers (76%) with the remaining from Genetic Counselors (GCs, 24%). The main referral source from physicians and APPs were from the breast oncology program at MCC (224, 19%), and other large referral groups include the gynecology and endocrine oncology programs at MCC. This referral bases transitioned through the establishment of the program. In the first 12 months, 49% of the referrals came from Genetic Counselor service group within the institution. The genetic counseling service belongs to the same department as GH clinic, thus the referral benefited from the high level of awareness and direct referral after identification of genetic mutation through genetic testing. The awareness of GH service gradually spread through the institution and community, resulting in increased referral from non-genetic counselor sources.

Within the patient population, most underwent comprehensive panel genetic testing and some had targeted genetic testing. There were PV carriers of 46 different genes,[1]* with 36 individuals carrying PVs in more than one gene. Most patients were carries of PV of *BRCA1* and *BRCA2* genes (120 and 146, respectively), followed by *CHEK2* (70), *ATM* (51), *PMS2* (35) and *TP53* (30). Lynch syndrome genes account for 104 patients, with *PMS2* included.

The majority of patients (483, 58.8%) had a current or prior cancer diagnosis of the following organs at the initial presentation in GH, with the remainder of patients having no history of cancer at the time of their first visit: brain, breast, bladder, cervix, colon, eye, head and neck, kidney, leukemia, lung, lymphoma, neuroendocrine, ovary/fallopian tube/peritoneum, pancreas, prostate, soft tissue sarcoma, thyroid, and uterus. Skin cancers were not consistently documented in this report. The most common types of first primary cancer were: breast (244), colon cancer (42), ovarian/fallopian tube/peritoneal cancer (28), uterine (19), and thyroid (18). One hundred and thirty-five individuals had a history of two or more primary cancers.

Table 1. Distance travelled by patients.

FL county driving distance from MCC (miles)	Number of Patients (%)
>300	7 (.09%)
200-300	24 (3.1%)
100-199	94 (12.2%)
50-99	84 (10.9%)
<50	442 (57.3%)
Unknown FL county	121 (15.7%)
Total	772

Cancer treatment modalities and timing of treatment of these patients were evaluated. During the 42-months, the majority of patients were greater than 5 years since completion of therapy for their cancer (58%), with 26% of all patients less than 5 years, with the remaining 16% in active therapy for a cancer, such as surgical, radiation, or systemic treatment. Many patients had previously undergone preventive surgery which could reduce their risk of cancer development secondary to their mutation. For example, approximately 40% of those with increased breast cancer risk having completed bilateral mastectomy by the time of their first visit in GH.

Regarding provider demographics, more patients were evaluated by a physician at 836 visits compared to the advanced practice nurse (APN) with 571 visits. Of all of these visits the physician saw a majority of the new and new established patients compared to the APN (663, 47.1% vs. 158, 11.2%), while the APN saw more established patient visits than the physician (413, 29.3% vs. 173, 12.3%).

Patient demographic showed that the majority of patients evaluated in GH resided in Florida (772, 94%). Within the state of Florida, most patients (226, 27.5%) were from Hillsborough Country, FL (where MCC is located), 233 (28.4%) were from the 4 counties bordering Hillsborough county (Manatee, Pasco, Pinellas and Polk). One hundred and four (12.6%) were from Florida counties 100 miles or more away from MCC. The farthest county in Florida patients visited from was Santa Rosa county (N=3), which is approximately 445 miles from Moffitt (Table 1). Outside of the state of Florida patients were seen from 14 other states and Puerto Rico. Patients were also evaluated from international sites as well (Cayman Islands, Cuba, Peru, and the Virgin Islands). The patient population showed a range of health insurance coverage with a majority registered with private insurance (HMO or PPO, 467), followed by Medicare (95), Medicare managed care (46), Medicaid (17), Medicaid managed care (28), charity care (20), commercial (3), and private pay (2).

Discussion

To our knowledge, the GH clinic represents a novel clinical service, focused on comprehensive cancer surveillance across a wide spectrum for individuals with germline cancer predisposition. The clinic utilizes a holistic approach by integrating all cancer screening. GH encompasses both high risk and average risk surveillance, with a strong emphasis on serving as a care "home" to coordinate surveillance, even if some surveillance must be performed in the community outside the institution. There is a paucity of established clinics providing this type of comprehensive care for patients with different types of genetic mutations in one location. Clinics such as those providing care for *BRCA1* and *BRCA2* (*BRCA1/2*) specific mutations have shown success in providing a holistic support service with annual or biannual clinic visits incorporating proper screening, consideration of preventative risk-reducing surgery, timing of surgery with consideration of physiological and psychological concerns, chemo-preventative options, and clinical trial participation.[3] While these clinics can provide a comprehensive approach for a single cancer predisposition, for many cancer risk predisposition genes there are often more than one type of cancer that the patients are at increased risk to develop.

Patients who are actively undergoing treatment for cancer can face similar difficulties. For patients on active therapy for cancer in one organ, the cancer screening for other organs can frequently be found to be delayed and not completed on time. For any patients with ongoing active cancer treatment, GH continues to play an important role for discussing various cancer risks and screening/surveillance strategies for both the patients and their families. These barriers patients facing were identified early in the inception of GH and the coordination of such screening efforts for all potential cancer risks became a vital part of the GH clinic.

Patients in the GH clinic have directly benefitted from improved access to testing and are often offered expanded testing to further evaluate their cancer predisposition following the targeted testing for their underlying cancer. As all the above factors lead to the identification of more clinically actionable genetic mutations, the need for clinics such as GH increases steadily.

Based on the experience in GH, we found majority of the patients underwent cancer predisposition genetic testing meet the genetic testing criteria illustrated in NCCN guidelines. However, due to the increased utility of panel genetic testing, it is not unusual to find a genetic mutation unsuspected based on family history. For example, *PMS2* gene is not known to

have significantly increased risk to develop breast cancer. A patient may undergo genetic testing for the purpose of breast cancer risk, but a *PMS2* gene mutation can be discovered instead. Such scenario is not unusual and may be expected under certain circumstance owing to small family structure. A woman carrying a *PMS2* gene mutation has approximately 15% chance to develop colon cancer in lifetime.[4] In the meantime, her risk to develop breast cancer may be as high as 30% in lifetime if there is a significant family history of breast cancer resulted from polygenetic risk conferred by common genetic alleles.[5] The chance may be even higher when additional nongenetic factors are counted, for example, early menarche, nulliparity, or high density of the breast (https://ibis.ikonopedia.com/; https://bcrisktool.cancer.gov/).[6-9]

When actionable genetic mutations are identified, providers must be aware of which, if any, advanced cancer screening tests their patient is a candidate for. Surveillance and management guidelines for some known deleterious mutations were created by National Comprehensive Cancer Network (NCCN). Cancer genetic specialists play an important role on interpreting complex results from panel testing, as well as providing means for follow up and surveillance of patients with known PVs. This has been incorporated into the care of patients in GH. While some mutations are identified in patients who are in the age range of increased risk for developing malignancy, many are identified prior to the rise of risk. This is reflected in the variation of visit frequency in our patient population. Many patients may only require an annual visit for review of family history, physical exam, and updated guidance on screening guidelines. Other patients require a more robust approach to screening with an increased frequency of visits based on screening guidelines, or a return visit for a new complaint, or a return visit for additional genetic testing based on new personal or family history. As an example, a high-risk breast cancer patient often visited GH twice a year for physical examination and alternating mammography and breast MRI. Similarly, complex cases such as Li-Fraumeni syndrome or Cowden syndrome patients were recommended to visit twice a year even after bilateral mastectomy. They might visit sooner if situation indicated. In the meantime, a large portion of the patients (50%) had one visit for a consultation, then decided to follow with other providers for future surveillance due to the logistics or according to their preferences.

The intention of GH is to be widely accessible to patients carrying PV with cancer predisposition within the cancer center, as well as from the community. Evaluating the demographics of the patients seen in GH helped identify the catchment area and diversity in our patient population. As was expected, most of the patients seen in GH presented from Hillsborough county where MCC is located, and its four neighboring counties. Predominately, referrals came from providers within MCC which largely contributed by the fact that patient access to the genetic counseling within MCC has been integrated broadly and efficiently. All patients who are candidates for genetic testing or patients who request to be referred are given appointments for genetic counseling. Patients with PVs may then be given a referral to be seen in GH. This approach helps streamline the genetic service needed and reduce undue delays in patient care.

GH was established to be the main clinical "home" for these patients so that they may have succinct and appropriate cancer surveillance coordinated according to the PV. In general, studies has demonstrated that appropriate referrals for hereditary cancer evaluation to genetics professionals continue to be low, only 34% of breast cancer patients, 13% of uterine cancer patients and 15% of ovarian cancer patients meeting guidelines for referral were actually referred by their healthcare providers.[2] In order for patients to benefit from the services offered by GH and similar clinics, more providers must be aware of the advantages of proper surveillance and coordination in a comprehensive cancer predisposition clinic like GH, and subsequently make a referral for these patients to be seen.

Generally, genetics providers are limited to larger academic centers potentially making access difficult for patients living in smaller communities or remote areas. Telehealth platforms can facilitate the access and medicine has recently made a major shift to telehealth due to the COVID-19 pandemic. This has been enhanced by policy changes during the COVID-19 pandemic to reduce barriers to telehealth access.[10] Telehealth visits are frequently utilized at MCC, and promotion of this convenient modality of patient care will allow GH and similarly developed clinics to reach a wider geographic catchment area. This has been a great advantage to our patient populations who live a significant distance from our center as highlighted in Table 1.

For facilities seeking to establish a clinic similar to GH, there were several lessons learned that would be important to incorporate. Patients with genetic risk for multiple types of cancer bear significant burden in their personal life, work life, psychological health and financial health. A recognizable number of patients experience screening avoidance or fatigue at the beginning or subsequently during the follow up. A significant portion of their relatives do not respond to the recommendation of familial cascade genetic testing. We expect screening and familial genetic testing compliance can benefit from continuous education and counseling in follow up visits. Very often, over amplified anxiety toward cancer risk can be eased with continuous counseling as well. Regarding insurance coverage, providing these genetic services under the supervision of an attending physician helped ease the insurance coverage of services that may ordinarily be difficult to be supported with reimbursement solely under the care of a genetic counselor. Identifying disease specific referral partners within your own or partnering institutions will be critical for patients to benefit from efficient care coordination when additional screening services (eg endoscopies) or treatment are needed. Raising awareness of the program within your institution and surrounding catchment area is critical as well. We have often found that providers in the community or our own

institution are eager to refer patients to GH after they became aware of the level of comprehensive services provided in GH. All efforts on establishing patients in a comprehensive screening program can not only help educate patients about their risks, but also ensure early identification of any cancers that may develop as a result of their genetic mutations.

Since the establishment of the clinic, new visits increased steadily and significantly. In the first 12 months, 49% of the referrals came from Genetic Counselor service group within the institution. Eventually, 42 months overall referral from GCs decreased to 24% while the total referral increased dramatically. The genetic counseling service belongs to the same department as GH clinic, thus the referral at the beginning of establishment benefited from GCs high level of awareness and direct referral after identification of genetic mutation in genetic counseling service. The awareness of GH service gradually spread through the institution and community, resulting in increased referral from non-genetic counselor sources. The awareness may also have been benefited from brief in-service presentations provided by GH provider during tumor boards or administrative meetings hosted by other departments or services within the cancer center.

We suspect that, over time, even more patients will be referred for genetic testing. Societies, such as the American Society of Breast Surgeons, have released consensus guidelines suggesting that all patients with a personal history of breast cancer be tested for hereditary breast cancer.[11] The demand for comprehensive services provided by GH clinic will continue to rise.

Conclusion

Due to the ease and accessibility of panel genetic testing, more patients than ever before being tested for cancer predisposition genes, requiring skilled genetics professionals to interpret results and provide proper guidance. Patients who are found to have a genetic cancer predisposition tend to be at high risk for multiple cancers, which all require the appropriate screening, surveillance, and coordination of care. GH is a novel model for genetic high risk cancer surveillance, providing complete and cohesive genetics care by ensuring that patients have comprehensive surveillance for their genetic mutation. GH has been widely accepted by patients and providers and provides a valuable service to patients who carry a genetic PV predisposing to cancer.

Author Contributions

Each author has significant contribution to at least one of the following task: (1) Conception, design, data acquisition, analysis or interpretation of data; (2) Drafted the work or revised it critically for important intellectual content; (3) Approved the version to be published.

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Ethical Approval

Work related to this manuscript was approved by Moffitt Cancer Center institutional review board.

Consent to Participate

Consent for chart review data is waived based on institutional and national human research standard.

Informed Consent

All listed authors approved this manuscript for publication. All agreed to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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Note

1. *APC, ATM, BAP1, BARD1, BMPR1A, BRCA1, BRCA2, BRIP1, CDH1, CDKN2A, CHEK2, DIS3L2, EGFR, EPCAM, ETV6, FANCD2, FH, FLCN, MEN1, MITF, MLH1, MSH2, MSH6, MUTYH, NBN, NF1, NF2, PALB2, PIK3CA, PMS2, POLD1, POT1, PTEN, RAD50, RAD51 C, RAD51D, RB1, RET, SDHA, SDHB, SDHC, STK11, TP53, TSC1, TSC2, VHL.*

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