

A Comprehensive Cancer Risk Management Clinic for Families With Hereditary Cancer Syndromes

Outcomes After 6 Years



IN BRIEF

In recent years, there has been an increase in completing genetic testing for hereditary cancer syndromes, resulting in more individuals and families needing long-term cancer risk management. Within Aurora Health Care, genetic counselors noted discrepancies between cancer risk management recommendations and published guidelines, inconsistent adherence to cancer risk management recommendations, and limited cascade testing. To address these gaps in care, the health system developed its hereditary cancer center, a clinic staffed by a medical oncologist, cancer nurse coordinator, genetic counselors, and support staff. Over a 6-year period, 889 patients and relatives established care at the hereditary cancer center. Each patient learned of their cancer risk(s) based on their genetic testing results, cancer risk management plan, and recommendations for lifestyle modification. Longitudinal care is provided by the Hereditary Cancer Clinic, and data are collected to track several outcomes. Outcomes include diagnosing a biallelic disorder in a child, reclassifying a variant of uncertain significance as pathogenic or likely pathogenic, removing or clarifying a diagnosis, and diagnosing early-stage cancer or neoplasm. All cancers diagnosed by the hereditary clinic were at stage II or less. This approach to hereditary cancer management results in standardized hereditary cancer risk management and positive health outcomes. Data from this manuscript were presented at the National Society of Genetic Counselors Annual Conference in November 2020.

Hereditary cancer predisposition syndromes are common health conditions. An estimated 1 person in every 400 individuals has a pathogenic variant (or “mutation”) in *BRCA1* or *BRCA2*,^{1,2} and 1 person in every 280 individuals has a pathogenic variant in *MLH1*, *MSH2*, *MSH6*, or *PMS2*.³ The prevalence of these conditions is even higher for those with a diagnosis of breast, ovarian, colon, or uterine cancer.⁴⁻⁷ In addition, there are multiple other genes linked to hereditary risks for cancer.^{3,6} The prevalence of pathogenic variants in moderate penetrance genes may be even higher than the prevalence of pathogenic variants in high penetrance genes, collectively making these conditions common.^{3,8}

Genetic testing for hereditary cancer syndromes increased in popularity following several events in the early 2010’s, such as the *Association for Molecular Pathology v Myriad Genetics* US Supreme Court decision,⁹ Actress Angelina Jolie’s op-ed in the *New York Times*,^{10,11} increasing availability of next-generation sequencing testing and multigene panels,^{8,12-15} and decreasing testing-related costs.^{12,14,16} As a result, more individuals are being identified as having a hereditary cancer syndrome and requiring long-term, multiorgan risk management.¹¹

With the increasing uptake of multigene panels, genetic counselors report less depth of information needed in pretest counseling appointments about the risks and management associated with cancer and the individual genes on a panel, as they can now focus more on the breadth of the panel.¹³ Due to increasing demands for genetic counseling,^{11,13} many disclosures of one’s testing result occur via a 1-time

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telephone call or post-test visit,¹³ whereas a positive genetic testing result affects patients’ decision-making over the lifetime.¹⁷ In addition, our understanding of cancer risks and optimal management changes over time.¹⁴ Without having a provider dedicated to the management of one’s hereditary cancer syndrome, patients may not be informed of updated management recommendations. Long-term management of hereditary cancer syndromes often falls to patients’ primary care provider or the physician who referred them to genetic counseling. Primary care providers have demonstrated a knowledge gap about the management of *BRCA1* and *BRCA2* and report feeling uncomfortable with cancer risk management due to the rapidly changing landscape of genetics.^{4,18} Patients also report that they receive differing

or incorrect medical management recommendations from their non-genetics providers.^{18,19}

The Hereditary Cancer Prevention and Management Center

With the above challenges in mind, the Aurora Health Care Department of Genomic Medicine developed the hereditary cancer center, which is formally known as the Hereditary Cancer Prevention and Management Center. Aurora Health Care is part of Advocate Aurora Health, an integrated health care system in northern Illinois and eastern Wisconsin. It employs 11 genetic counselors to staff multiple subspecialty clinics. Aurora Health Care sees more than 7500 new patients with cancer each year, and its genetic counselors identify as many as 200 individuals per year as having a hereditary cancer syndrome. Prior to the development of the hereditary cancer center, patients were referred to genetic counseling for comprehensive pretest counseling. In addition to disclosing their testing results, the genetic counselor would provide patients with published medical management guidelines if they tested positive for a hereditary cancer syndrome. These recommendations were routed to the referring provider to manage the patient's cancer risk(s). This model is like those reported in Hooker et al¹³ and Puski et al¹⁷. Genetic counselors also recommended testing for patients' relatives at the time of results disclosure. Relatives of a proband (ie, a person serving as the starting point for the genetic study of a family) seen at Aurora Health Care would obtain a separate referral to genetic counseling from their provider. If positive, the relative would then receive long-term management from their referring provider. This pathway can result in inconsistent recommendations for cancer risk management among patients and their relatives.

The Aurora Health Care hereditary cancer center is a multidisciplinary clinic with the mission to "address the prevention and cancer risk management of patients and their at-risk relatives with hereditary cancer conditions by providing continuity and coordination of care." Similar clinics have been created around the world with reported positive patient outcomes.²⁰⁻²⁵ The following is a summary of the hereditary cancer center's development, clinic workflows, patient volumes and demographics after 6 years, and specific patient outcomes.

Clinic Development and Workflow

Prior to the inception of the program, the medical oncologist and cancer nurse coordinator of the hereditary cancer center attended City of Hope's Intensivist Course in Genomic Cancer Risk Assessment to ensure the base knowledge necessary for managing complex hereditary cancer syndromes. The oncologist and nurse coordinator then worked with genetic counselors to:

- Create an Epic order for referrals and schedules for the clinic
- Identify workspaces
- Outline a workflow
- Define documentation requirements and ownership
- Develop a case conference format
- Research video conference resources for remote participants (ie, referring providers, genetic counselors)

As the caseload grew, the team identified opportunities to better serve patients with hereditary cancers. For example, the hereditary cancer center partnered with radiology to establish a whole-body MRI protocol

(eg, for patients with Li-Fraumeni syndrome, hereditary paraganglioma, and pheochromocytoma syndrome, among others) and a dedicated MRI screening of the pancreas. The team also partnered with gastroenterology to identify physicians skilled in advanced endoscopic techniques and interested in hereditary cancer screening. The clinic was originally held twice per month at a tertiary facility in Milwaukee, Wisconsin. Since then, the clinic has expanded to a weekly occurrence, with the addition of a monthly clinic in Green Bay, Wisconsin.

At clinic appointments, patients learn about their hereditary cancer syndrome and participate in shared decision-making regarding their cancer risk management. The hereditary cancer center team stays current on evolving management guidelines and supervises longitudinal management.

The hereditary cancer center is formatted as a multidisciplinary clinic. The first hour is dedicated to a team review of the cases being seen that day. Initial consultations are scheduled as a 90-minute appointment per new family unit. The proband is the focus of the visit, and time is initially spent updating their medical, surgical, and family history. The medical oncologist and genetic counselor provide education regarding the identified variant and appropriate screening or risk-reducing measures. Case identification and subsequent genetic testing for family members is then offered. Identified screening tests and referrals for risk-reducing surgery are managed by this team. Healthy lifestyle modifications are also reviewed and encouraged. A physical exam may be done based on patients' germline variant and age. Once patients are established in the clinic, follow-up appointments are typically 30-minutes every 6 months to 12 months to review screening tests, perform a physical exam, and update their personal and family history. Figure 1, page 41, illustrates the clinic workflow.

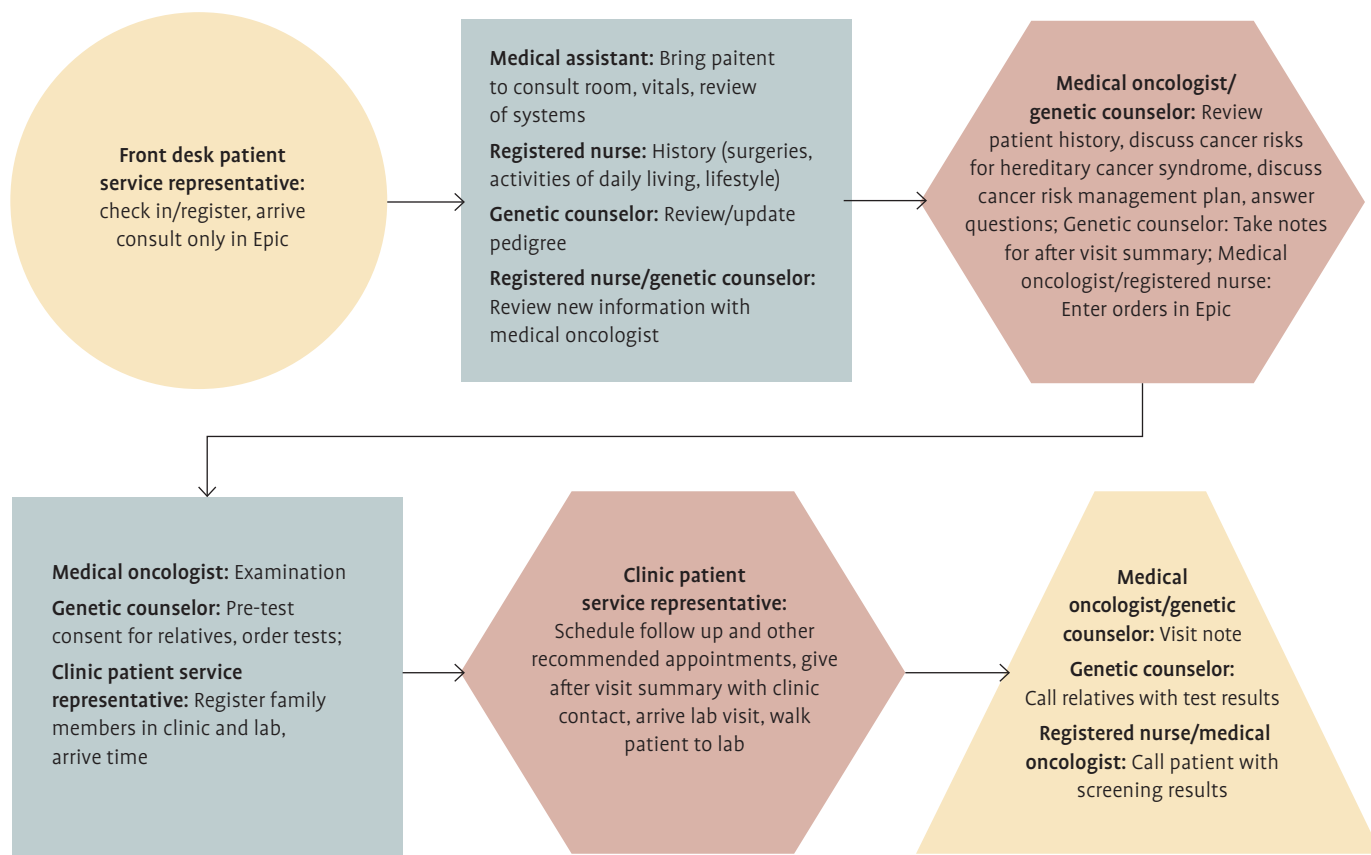
Most patients seen in the clinic are referred by the genetic counselor at the time of results disclosure. The hereditary cancer center team works extensively to present information about the center to multiple internal referral sources, as well as to other health care organizations. This practice has resulted in referrals from Advocate Aurora Health medical oncologists and primary care providers, as well as from external genetic counselors.

Study Demographics

From May 2015 to December 2021, 889 individuals established their care in the hereditary cancer center; 716 were assigned female at birth, and 173 were assigned male at birth. The average age at presentation to the clinic was 48.9 years (range, 4 years to 84 years).

The primary indication for referral is the identification of a genetic variant associated with elevated cancer risk. In total, 731 patients

Figure 1. Hereditary Cancer Center Workflow



had a positive genetic test result or a clinical diagnosis of a hereditary cancer syndrome. Further, 39 of the 731 patients had pathogenic variants in 2 or more genes (not including autosomal recessive conditions). Patients with 51 unique gene indications were seen (see Figure 2, page 59). Other indications for referral include a family history of a pathogenic variant, provocative family history with no pathogenic variant identified, pancreas cancer screening, and other/miscellaneous conditions.

Of the 889 patients who established care with the hereditary cancer center, 648 individuals were the first person in their family referred to the clinic (proband). A small proportion of the 241 non-probands already knew of their positive genetic test result when they presented to clinic, while most attended their relative’s appointment and established care with the clinic to be tested for the familial variant. Approximately half of all non-probands (n = 133) had a positive genetic test result; 94 individuals had a negative genetic test or only variant(s) of uncertain significance reported, while 10 individuals were not tested for various reasons and genetic testing was not recommended for 4 individuals.

Of the 731 patients with a positive genetic test result, 365 had a

prior diagnosis of cancer or neoplasm when they established their care with the clinic. The predominant cancer type was breast cancer. Another 23 patients had features of their condition (eg, polyposis in a patient with an APC pathogenic variant, pancreatitis in a patient with a PRSS1 pathogenic variant) without a diagnosis of cancer. Previvors—those at higher risk of cancer—accounted for 343 patients with a positive genetic test result.

Patients with a positive genetic test result underwent 233 risk-reducing surgeries (either risk-reducing in an unaffected patient or risk-reducing combined with anticancer treatment) prior to being seen in the clinic. Another 62 risk-reducing surgeries occurred within a year of a patient establishing their care with the hereditary cancer center, and 13 risk-reducing surgeries occurred more than a year after the patient established their care.

There are several reasons why patients may not have pursued risk-reducing surgery. Sixty-six surgeries are not currently recommended due to the young age of a patient. Another 81 surgeries were recommended but are not currently desired by the patient. Finally, 424 patients have not had any risk-reducing surgery because it is not recommended for their hereditary condition.

Outcomes

The hereditary cancer center has been open for 6 years and has documented 33 outcomes for 30 patients in that time. These outcomes can be sorted into 4 categories.

One patient with a biallelic disease diagnosis. This patient presented to genetic counseling due to her family history of cancer. Multi-gene panel testing was performed, and a pathogenic variant in PMS2 was found. Genetic testing was recommended for her husband to determine his risk for constitutional mismatch repair deficiency syndrome since the couple was of reproductive age and had young children. A multi-gene panel for the husband also revealed a pathogenic variant in PMS2. The couple elected to have their 3 living children and an ongoing pregnancy tested for constitutional mismatch repair deficiency syndrome. One of the children was found to have both PMS2 pathogenic variants. Their child has since established care with pediatric providers for cancer screening.

Four patients with variants of uncertain significance were reclassified. Four patients had variants of uncertain significance identified, which were suspected to be pathogenic. The hereditary cancer center coordinated additional work-up of these variants, which resulted in the reclassification of the variants. This allowed for more accurate

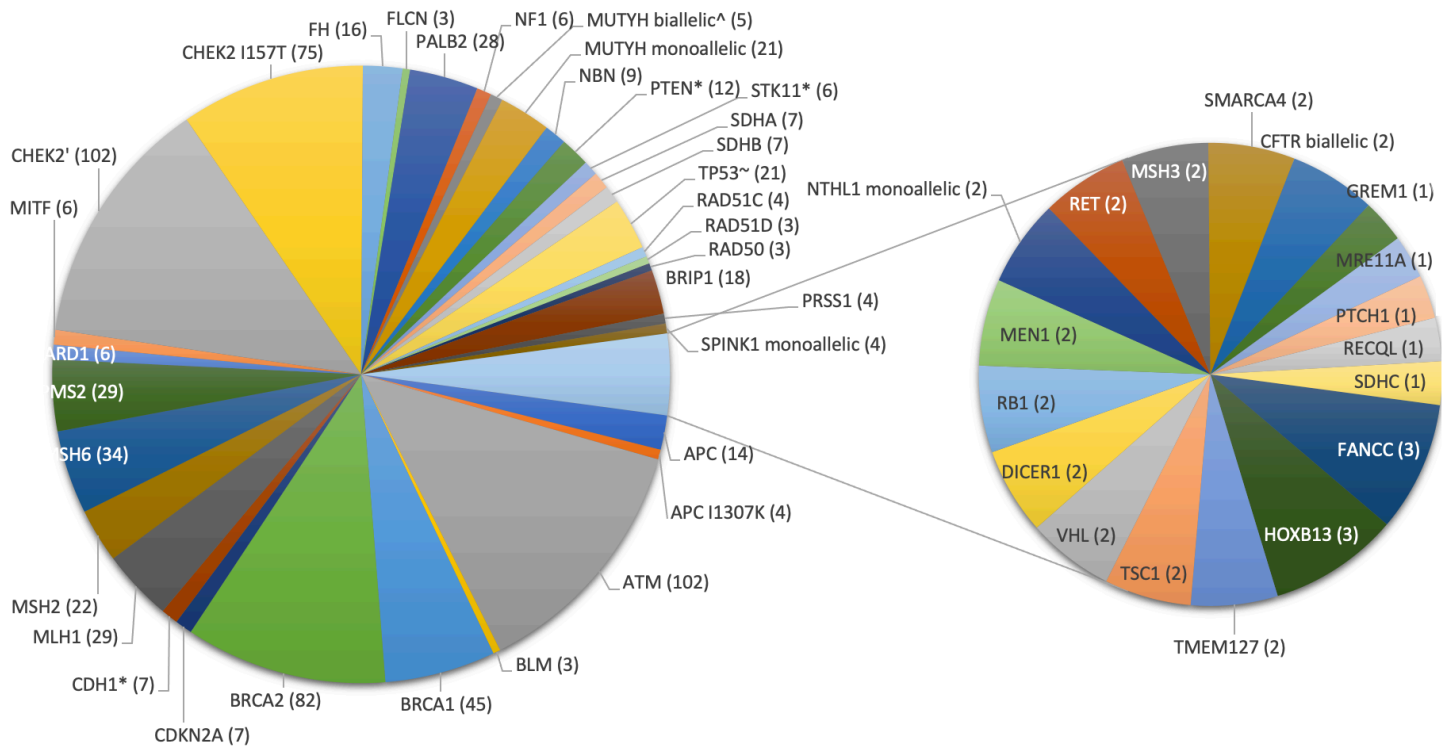
cancer risk assessment and identification of at-risk relatives.

One patient was referred for genetic counseling due to his personal history of colon polyps and family history of cancer. The patient also had a distant history of a single neurofibroma. An 81-gene panel revealed a variant of uncertain significance in NF1. He was later diagnosed with Stage IIA colon cancer and multifocal carcinoid tumors. A physical exam in the hereditary cancer center revealed 12 cafe au lait macules, with 9 measuring greater than 15 mm. The clinic recommended a referral to dermatology for multiple cutaneous nodules, 1 of which was a neurofibroma. This gave the patient a clinical diagnosis of neurofibromatosis type 1, and the lab used this information to upgrade the NF1 variant to being likely pathogenic.

Another patient was referred to genetic counseling for a personal history of colon polyposis. Genetic testing revealed a pathogenic variant in MUTYH and variant of uncertain significance in MUTYH. The phase of these variants could not be determined. The clinic then recommended genetic testing for the patient's mother, who was found to have the pathogenic variant. Since the variants were found to be in trans, the lab reclassified the uncertain variant as being likely pathogenic.

A third patient was found to have an amplification of exon 3 of

Figure 2. Gene Indications Seen at the Hereditary Cancer Center



* Indicates an individual with a clinical diagnosis. ^Indicates an individual with CHEK2 I157T in trans. ~Indicates three variants found to be not constitutional by skin punch biopsy. *Indicates an individual with three MUTYH variants.

the SDHB gene. The lab could not determine if the extra copies of exon 3 were in tandem and thus disrupting the gene sequence, or if they were located elsewhere in the genome. The report listed the variant as uncertain significance. The hereditary cancer center coordinated an additional blood sample from the patient and sent it for a gene-centric array comparative genomic hybridization. The amplified material was found in tandem, and the variant was classified as being likely pathogenic.

Most recently, a 25-year-old woman presented to the clinic due to the family history of polyposis in her father. She had a history of normal colonoscopies and previous, negative APC gene analysis. The hereditary cancer center coordinated genetic testing for her father, who was found to have a variant of uncertain significance in APC, c.531+3A>T (intronic), which can have an effect on splicing. Follow-up testing with RNA analysis was coordinated, and the variant was classified as being likely pathogenic. The female patient is now considered a true negative and can follow general population colon cancer screening guidelines.

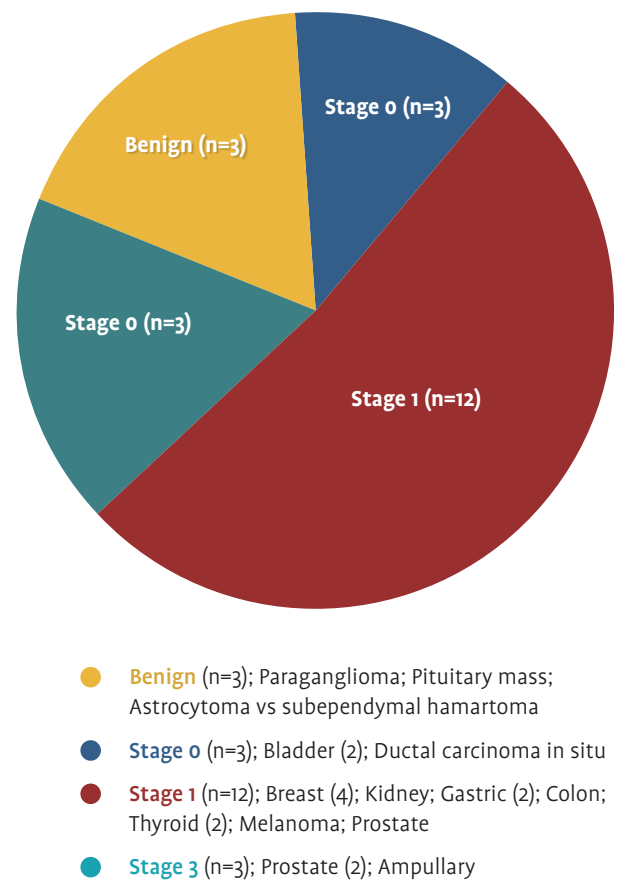
The clinic removed or clarified a diagnosis (n = 7). Seven patients had a diagnosis of a hereditary cancer syndrome that was removed or clarified by the hereditary cancer center. Three patients tested positive for pathogenic or likely pathogenic variants in TP53. The variants were reported as mosaic in 2 patients. Although the variant was reported as heterozygous in the third patient, his personal and family history did not meet modified Chompret criteria, and clonal hematopoiesis of indeterminate potential was suspected. These 3 patients initially elected to do cascade testing for their close relatives, which returned negative. Skin punch biopsies were obtained, and genetic testing was performed on cultured fibroblasts. All 3 patients tested negative for the TP53 variants on cultured fibroblasts, making a diagnosis of Li-Fraumeni syndrome unlikely.

Two patients were seen for genetic counseling in 2012 and 2013 for uterine cancer and a family history of cancer. Microsatellite instability testing by immunohistochemical staining on their tumors was abnormal. However, germline testing showed no pathogenic variants. Due to the patients' personal and family cancer history and abnormal tumor test, they were told to consider following Lynch syndrome screening guidelines. Paired tumor and germline molecular testing were performed in 2017 for 1 patient and in 2021 for the other patient. Again, no germline variants were identified. Although somatic testing did not identify 2 acquired pathogenic variants, the hereditary cancer center informed the patients that a diagnosis of Lynch syndrome due to an undetectable, germline pathogenic variant was unlikely.

Another patient was referred to the clinic for genetic counseling due to a family history of ovarian cancer. Genetic testing showed 3 pathogenic or likely pathogenic variants in MUTYH. The phase of these variants could not be determined. Family members were either unwilling to be tested, unavailable for testing, or uninformative. The patient completed a baseline colonoscopy, as recommended by the clinic, and had 28 tubulovillous and tubular adenomas. This clarified a diagnosis of MUTYH-associated polyposis.

Finally, a patient that was referred to the hereditary cancer center had patient-initiated research and genetic testing results that were positive for a germline variant in the 3' UTR of KRAS, which is

Figure 3. Cancers by Stage Diagnosed Through Screening Recommended by Hereditary Cancer Center



reported to be associated with breast, ovarian, and lung cancers. Based on her family history of cancer, clinical hereditary cancer testing was recommended to the patient. This testing returned negative for any pathogenic variants, and the patient was informed that she does not have a hereditary cancer syndrome.

Patients diagnosed with cancer (n = 21). An often-stated goal of the clinic is to minimize the impact of cancer on patients and their families through prevention and early detection. Since risk-reducing surgeries are not possible for all cancer types or not recommended for certain gene mutations, diagnoses of cancer are inevitable in this high-risk population. Nineteen patients were diagnosed with 21 cancers or benign tumors through screening recommended by the hereditary cancer center. The majority (n = 12) were diagnosed with cancer at Stage I, while no cancers were diagnosed at Stage III or IV. The cancer or tumor types and stages can be seen in Figure 3 (above).

Discussion

As genetic testing for hereditary cancer becomes standard of care for more indications, an increasing number of individuals are being

identified with hereditary cancer syndromes that require long-term cancer risk management.¹¹ Genetic counselors and other genetics providers often are not involved in the long-term care of these patients after coordinating testing and disclosing results.¹⁷ Management usually falls to the patients referring and/or primary care provider, who may not have a good understanding of hereditary cancer syndromes or the time to consistently seek updates to cancer risk management guidelines.^{4,19} To better address the needs of patients with hereditary cancer syndromes, Aurora Health Care developed the hereditary cancer center.

At clinic appointments, patients learn about their hereditary cancer syndrome and participate in shared decision-making regarding their cancer risk management. The hereditary cancer center team stays current on evolving management guidelines and supervises longitudinal management. Patients are referred to appropriate specialists (eg, gynecology-oncology, gastroenterology), and education and recommendations are shared with all providers involved in a patient's care. Finally, the clinic encourages cascade genetic testing and welcomes family members to attend the proband's appointment(s) to learn about the hereditary cancer syndrome and get testing if desired.

The hereditary cancer center's approach to hereditary cancer risk management has demonstrated several positive patient outcomes during a 6-year period. Diagnosing a biallelic disorder in the child of a patient, removing or clarifying a diagnosis of a hereditary cancer syndrome, or getting a variant of uncertain significance reclassified as pathogenic or likely pathogenic significantly changes the medical management for associated patients and/or their families. In some cases, patients are actually determined to not require high-risk cancer screening.

The most common outcome from the clinic was diagnosing a neoplasm related to an individual's hereditary cancer syndrome. Nineteen patients were diagnosed with 21 cancers through recommended cancer screening since 2015. While a diagnosis of cancer can feel inevitable in this high-risk patient population, it is reassuring that no cancers were diagnosed later than stage II for patients being seen by the hereditary cancer center. In fact, most cancers diagnosed by the clinic were found in stage I. This demonstrates that adherence with recommended screening, with the help and guidance of a knowledgeable care team, leads to better health outcomes for patients when diagnosed with a cancer.


Future Directions

Patients established with the Aurora Health Care Hereditary Cancer Prevention and Management Center are offered the opportunity to participate in research for which they may be eligible. The clinic team has already enrolled patients in several studies and continues to identify studies for which their patients may be eligible.

The hereditary cancer center hopes to expand geographically. Advocate Health Care in Illinois established 2 hereditary cancer centers in 2018 and 2020. This expansion will not only allow the clinic to serve more patients, but it will also allow for more robust data collection on patient outcomes and preferences.

Conclusions

The identification of a hereditary cancer syndrome provides an opportunity for cancer risk management. However, patients with

hereditary cancer syndromes may not undergo optimal risk assessment, screening, and risk-reducing management with a nongenetics provider. The hereditary cancer center is an effective model to care for patients with hereditary cancer syndromes. The positive patient outcomes from this clinic demonstrate the benefits of this model. 

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Disclosure of interest

The authors report no competing interests to declare.

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