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Beyond First-Degree Relatives: Unlocking the Genetic Insights from Extended Family History

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Abstract

In oncology, a thorough family history is a cornerstone of genetic risk assessment, yet it is often limited to first-degree relatives—parents, siblings, and children—thereby missing crucial hereditary patterns. This article highlights the importance of including extended family members, such as second- and third-degree relatives, in risk assessment to uncover hereditary cancer syndromes that might otherwise go undetected. This case exemplifies how extended family history can transform patient care by enabling accurate diagnoses, personalized treatment, and preventive strategies. Despite time constraints in clinical settings, tools such as targeted questioning, standardized questionnaires, and digital pedigree platforms can streamline the collection of a three-generation pedigree. Current guidelines from the American College of Medical Genetics and Genomics and National Comprehensive Cancer Network recommend such comprehensive histories, underscoring their clinical value. Incorporating extended family history should become standard practice in oncology to align with the principles of precision medicine and improve outcomes for patients and their families.

Keywords

- genetic screening
- extended family history
- oncology
- precision medicine
- hereditary cancer syndromes
- three-generation pedigree

Introduction

In oncology, a comprehensive family history is a cornerstone of genetic risk assessment, yet its full potential often remains underutilized. Traditionally, clinicians focus on first-degree relatives (parents, siblings, children) when evaluating hereditary cancer risk. While immediate family history is critical, a narrow focus can miss significant inheritance patterns that only emerge when second- and third-degree relatives are considered. For example, up to 30% of pathogenic mutations linked to breast cancer occur in women without a strong family history. This means many at-risk individuals might be overlooked if we ignore the broader family tree. Extended family history—including grandparents, aunts, uncles, nieces/nephews, and cousins—can reveal clusters of cancers or early-onset cases that first-degree history alone might not capture.[1,2] Identifying a hereditary cancer syndrome early can prompt life-saving enhanced screening or preventive measures for the patient and their relatives.

However, collecting a detailed three-generation pedigree in a busy clinic is challenging. Time constraints (studies show physicians spend on average < 3 minutes gathering family history in routine visits) and lack of standardized tools are major barriers. As a result, critical information about the patient's extended family is often not recorded. A U.S. survey found only about 31% of adults felt they knew their family's cancer history "very well," highlighting how often family history can be incomplete or inaccurate. This article addresses these gaps by exploring the clinical impact of extended family history in oncology, illustrating its value with a case study, reviewing current guidelines, and

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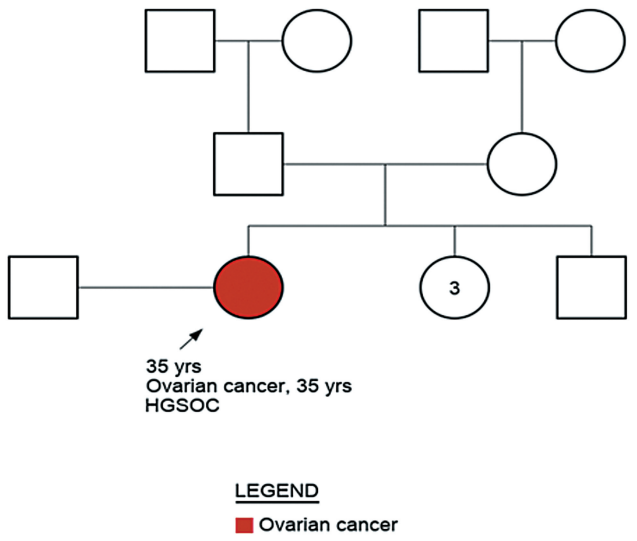

Fig. 1 Example of a pedigree with only first-degree relatives. Standard pedigree symbols are used (squares = males, circles = females, colored symbols indicate individuals affected by a certain condition "A").

describing practical tools (including digital pedigree platforms) to efficiently integrate extended family history into practice.

Case Example

Consider a 35-year-old woman diagnosed with high-grade serous ovarian carcinoma with no history of malignancy in first-degree relatives. Genetic testing revealed no BRCA1/2 mutations. Based on first-degree history alone, she does not meet the criteria for further testing (►**Fig. 1**).

However, a more detailed inquiry changes the picture. The patient recalls an extended family history: a maternal aunt was diagnosed with ovarian cancer at age 45, maternal uncle had colon cancer at 38, another paternal uncle had colon cancer at age 65, and paternal grandmother had endometrial cancer at age 50. These additional clues—ovarian, colon, and endometrial cancer on both the side of the family—are red flags for Lynch syndrome (hereditary nonpolyposis colorectal cancer). Lynch syndrome often involves colon, endometrial, ovarian, and other cancers across generations. Notably, having two or more relatives in the family with Lynch-associated cancers (e.g., one with endometrial, another with colorectal cancer, and another with ovarian cancer) greatly increases suspicion for this syndrome. The patient's first-degree relatives were cancer-free, but her second- and third-degree relatives suggested a pattern (►**Fig. 2**).

With this information, the care team pursued a broader genetic panel. A pathogenic MSH2 mutation was identified—confirming Lynch syndrome, which was initially missed when only first-degree relatives were considered. This diagnosis had profound implications: it explained the patient's ovarian cancer and indicated a high risk for other malignancies (like colon cancer) in her future and immunotherapy if required.[3] It also enabled cascade testing for her relatives. Several family members who would not have qualified for testing under narrow criteria were found to carry the same MSH2 mutation. They have since entered high-risk screening programs (e.g., colonoscopy at earlier ages and shorter intervals), a intervention which is proven to improve outcomes in Lynch syndrome by catching malignancies early.

Discussion

This case underscores the untapped value of extended family history. If we had adhered strictly to first-degree history, a heritable cancer syndrome would have gone undetected.

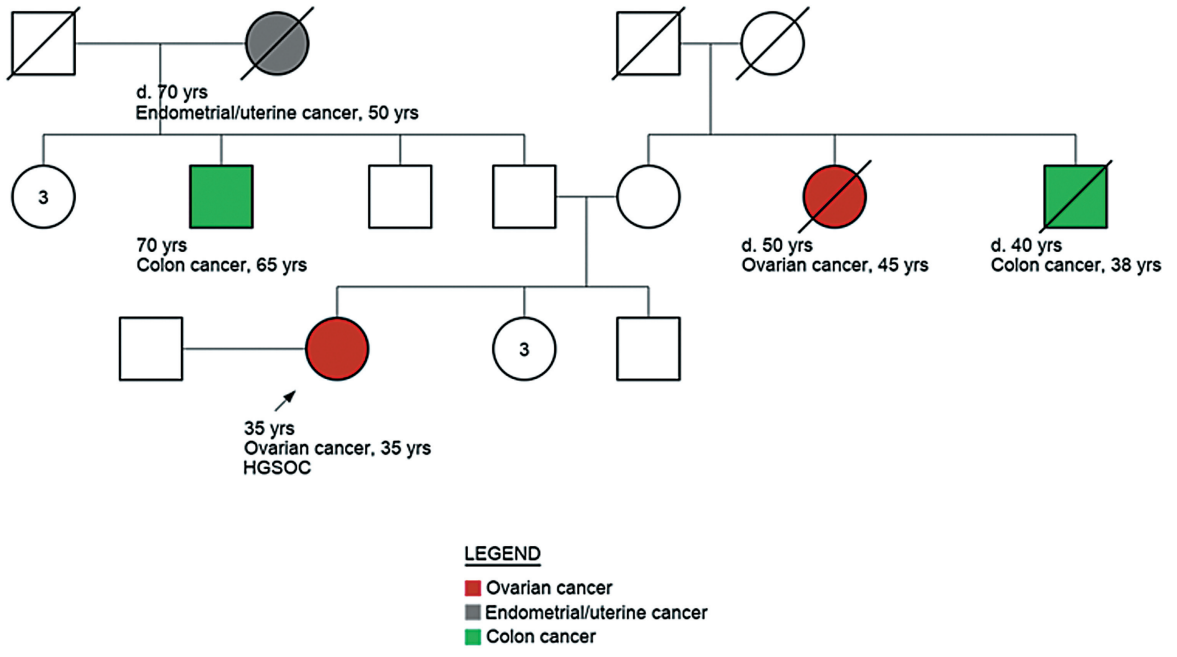

Fig. 2 Example of a pedigree with three generations.

Unfortunately, such scenarios are not rare. Many hereditary cancer cases fail to meet traditional testing criteria based on limited family data. For instance, criteria for BRCA1/2 testing heavily weigh early breast or ovarian cancer in close relatives—yet a significant proportion of BRCA mutation carriers lack an immediate family history of cancer (often because the mutation came paternally or through small families). Extended family history with at least three-generation pedigree thus directly impacted clinical care: enabling precision treatment (e.g., considering immunotherapy or pembrolizumab for MSH2-associated tumors) and appropriate surveillance for the patient, and predictive testing for her family.[2]

Professional guidelines in oncology strongly emphasize the collection of a three-generation family history for risk assessment. Both the American College of Medical Genetics and Genomics (ACMG) and the National Comprehensive Cancer Network (NCCN) recommend going beyond parents and siblings to include second- and third-degree relatives in the pedigree.[4] The ACMG/National Society of Genetic Counselors referral guidelines (2015) enumerate various "red flags" for inherited cancer syndromes—many of which involve patterns in the extended family (e.g., "two or more relatives with the same or related cancers, one of whom was diagnosed under age 50").[5] The NCCN guidelines for genetic/familial high-risk assessment (updated 2024) similarly advise documenting cancers in grandparents, aunts, uncles, nieces/nephews, and even great-grandparents or cousins if pertinent, as part of routine evaluation.[6]

Common hereditary cancer syndromes identified through such comprehensive histories include hereditary breast and ovarian cancer syndrome, most often caused by pathogenic variants in BRCA1 and BRCA2, which predispose to breast, ovarian, prostate, and pancreatic cancers; Lynch syndrome, associated with pathogenic variants in mismatch repair genes (MLH1, MSH2, MSH6, PMS2, and EPCAM), which increases the risk of colorectal, endometrial, gastric, and other gastrointestinal and genitourinary cancers; and Li–Fraumeni syndrome, caused by germline TP53 variants, which confer a high lifetime risk of sarcomas, breast cancer, brain tumors, adrenocortical carcinoma, and leukemia. Other well-recognized hereditary cancer syndromes include multiple endocrine neoplasia type 2 (MEN2) (RET mutations), associated with medullary thyroid carcinoma, pheochromocytoma, and parathyroid tumors; neurofibromatosis type 1 (NF1) and type 2 (NF2), predisposing to nerve sheath tumors, optic gliomas, meningiomas, and vestibular schwannomas; retinoblastoma (RB1 mutations), associated with early-onset eye tumors and increased risk for osteosarcoma and soft tissue sarcoma; Wilms tumor predisposition syndromes (e.g., WT1 mutations, Denys–Drash syndrome, Beckwith–Wiedemann syndrome); and polyposis syndromes such as familial adenomatous polyposis (FAP) (APC mutations) and MUTYH-associated polyposis (MAP) (MUTYH mutations), both increasing risk for colorectal and extracolonic cancers.

These syndromes can often be suspected through a detailed family history and subsequently confirmed by germline genetic testing—such as next-generation sequencing using hereditary cancer panels—to determine an individual's inherited risk. Depending on the clinical context, testing strategies may range from targeted multigene panels to more comprehensive approaches like whole-exome sequencing or whole-genome sequencing.

Collecting a detailed extended family history not only aids in identifying potential hereditary cancer syndromes or pathogenic genetic variants within a family but also guides subsequent management. When the proband is found to carry a pathogenic or likely pathogenic variant, this information enables cascade testing of at-risk relatives, facilitating timely risk stratification, implementation of targeted surveillance strategies, and initiation of preventive interventions. At every stage, genetic counseling plays a pivotal role in ensuring informed decision-making, addressing ethical considerations such as confidentiality and possible discrimination, and providing psychological support to alleviate anxiety and promote adaptive coping.

Tools and Best Practices for Collecting Extended Family History

Gathering extensive family history in a busy clinic can be daunting. However, several strategies and tools can streamline this process:

- Targeted questions ("Verbal Autopsy"): Rather than a generic "Any family history of cancer?," ask specific, pointed questions to jog patients' memory. For example: "Have any relatives (including grandparents, cousins) had cancer before age 50?" (Early-onset cancers in the family are red flags.) "Has anyone in your family had multiple cancers or bilateral cancers?" (E.g., someone with cancer in both breasts, or colon and endometrial cancer – suggestive of hereditary syndromes.) "Are there any histories of unusual cancers or tumors in your extended family, like male breast cancer or rare cancers?" (These can be clues to specific mutations.) "Any instances of colon polyps, young strokes (which might indicate MSH2-associated Muir–Torre syndrome), or other conditions in the family?"

Such focused questions function as a verbal checklist, ensuring the patient thinks beyond immediate relatives. Patients may not volunteer that "Grandpa had colon cancer at 45" unless specifically prompted about grandparents or early ages.[7]

- Use of family history questionnaires (FHQs): Previsit or in waiting rooms, patients can fill out a family history form. Standardized FHQs capture relatives' ages, health issues, and ages at diagnosis. These forms can be paper or electronic. Studies show that structured questionnaires substantially improve the quantity and quality of family history data recorded, compared to unprompted clinician interviews.
- Digital pedigree tools: Several digital platforms allow patients and providers to collaboratively build a pedigree.

For example, the Invitae Family History Tool and platforms like Progeny or FamGenix enable patients to enter their family data through a secure online interface, which then generates a pedigree chart and risk assessment analysis.[8]

When possible, drawing even a rough three-generation family tree during the consultation is incredibly valuable. As the saying goes, "a picture is worth a thousand words"—visually mapping out relationships and cancers often reveals patterns one might miss in text. The key is to incorporate the extended family routinely, not just stop at parents and siblings.

In the current era of artificial intelligence (AI), technology offers new possibilities for enhancing family history collection and utilization in oncology. AI-driven tools can automate patient history intake through digital questionnaires, detect missing or inconsistent information, and integrate these data with genomic and clinical databases to generate personalized risk assessments. Incorporating such capabilities into electronic medical records allows for interactive pedigree charts that can be updated in real time, shared across multidisciplinary teams, and linked to laboratory and imaging results. This integration will not only streamline clinical workflows but will also ensure that family history remains a dynamic and actionable component of precision cancer care.

To integrate extended family history into genetic risk assessment in oncology practice, consider the following structured approach (►**Fig. 3**):

Also, encourage communication of genetic findings to extended family, so that relatives who may also be at risk can undergo testing and prevention. This process is cyclical revisit of the family history periodically as the family evolves and update recommendations accordingly.

By following these steps, the care team ensures that an extended family history truly informs patient care at every juncture, from risk stratification to intervention. It transforms a pedigree from a static record into a living tool that guides dynamic decision-making in oncology.

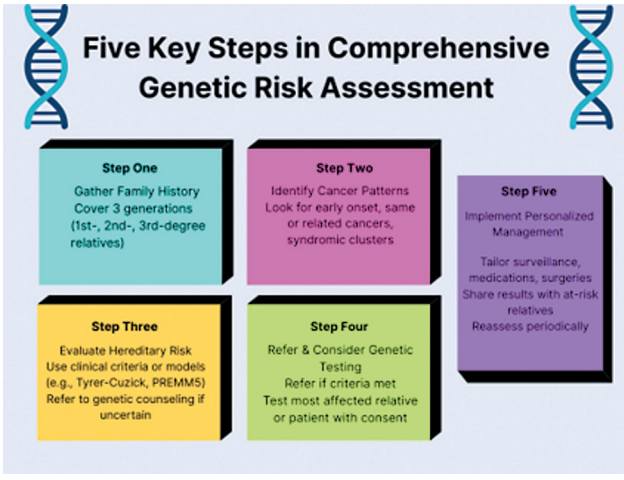

Fig. 3 Five key steps in comprehensive genetic risk assessment.

Conclusion

Limiting genetic risk assessment to first-degree relatives is outdated and risks missing hereditary cancer syndromes. Extended family history offers valuable insights that can uncover hidden risks and guide more precise care. As shown in our case, deeper pedigree analysis enabled appropriate testing and intervention. Today's tools and team-based approaches make comprehensive family history easier to implement, even in busy clinics. Embracing this broader view empowers not just individual patients but entire families, aligning with the goals of precision medicine. It is time to make extended family history a standard part of cancer risk assessment.

Call to Action

Start today. In your next patient encounter, go beyond the basics—ask about grandparents, aunts, uncles, and cousins. Consider developing a simple worksheet or adopting an electronic family history tool in your practice. If you already gather family history, make it a habit to update and delve deeper whenever possible. By doing so, you may uncover critical insights that alter the patient's preventive or therapeutic plan for the better. As the adage in genetics goes, "the family history is still the cheapest genetic test." Let us use it to its fullest extent in the fight against cancer.

Authors' Contributions

Study conception and design: A.R. and R.S. Manuscript writing: A.R. and A.K. Critical review of manuscript: A.K. and R.S. Approval of final article: All authors. Accountability for all aspects of the work: All authors.

Patient Consent

Patient consent is not applicable as no patient data, clinical details, or identifiable information are included in this report.

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Conflict of Interest

None declared.

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References

1 Guttmacher AE, Collins FS, Carmona RH. The family history–more important than ever. N Engl J Med 2004;351(22):2333–2336
2 Wattendorf DJ, Hadley DW. Family history: the three-generation pedigree. Am Fam Physician 2005;72(03):441–448
3 Holter S, Hall MJ, Hampel H, et al. Risk assessment and genetic counseling for Lynch syndrome - practice resource of the National Society of Genetic Counselors and the Collaborative Group of the

Americas on Inherited Gastrointestinal Cancer. J Genet Couns 2022;31(03):568–583. Doi: 10.1002/jgc4.1546
4 Daly MB, Pal T, Berry MP, et al; CGC CGC LCGC CGC CGC. Genetic/familial high-risk assessment: breast, ovarian, and pancreatic, version 2.2021, NCCN clinical practice guidelines in oncology. J Natl Compr Canc Netw 2021;19(01):77–102
5 Hampel H, Bennett RL, Buchanan A, Pearlman R, Wiesner GLGuideline Development Group, American College of Medical Genetics and Genomics Professional Practice and Guidelines Committee and National Society of Genetic Counselors Practice Guidelines Committee. A practice guideline from the American College of Medical Genetics and Genomics and the National Society of Genetic Counselors: referral indications for cancer predisposition assessment. Genet Med 2015;17(01):70–87
6 National Comprehensive Cancer Network. NCCN Clinical Practice Guidelines in Oncology: Genetic/Familial High-Risk Assessment: Breast, Ovarian, and Pancreatic, Version 2. 2024; and Colorectal, Version 1. 2023. Accessed 2025 at: https://www.nccn.org
7 Qureshi N, Carroll JC, Wilson B, et al. The current state of cancer family history collection tools in primary care: a systematic review. Genet Med 2009;11(07):495–506
8 Bucheit L, Johansen Taber K, Ready K. Validation of a digital identification tool for individuals at risk for hereditary cancer syndromes. Hered Cancer Clin Pract 2019;17:2

