Lynch Syndrome: Why Are Families Still Missing Cascade Testing?

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> Lynch syndrome, a hereditary cancer predisposition, significantly increases lifetime risks for colorectal, endometrial, and other cancers. Identifying individuals with pathogenic variants is only the first step; cascade genetic testing of at-risk relatives is critical for maximizing preventive benefits. But uptake of this vital screening remains stubbornly low, leaving many families vulnerable.1

KEY TAKEAWAYS

- The Pivot: Cascade testing uptake for Lynch syndrome is not uniform, varying significantly by family structure and the initial proband's characteristics.
- The Data: First-degree relatives of probands with pathogenic variants had a 2.5-fold higher likelihood of cascade testing compared to second-degree relatives (OR 2.5; 95% CI, 1.8-3.4; PThe Action: Clinicians should actively engage with probands to identify and facilitate testing for all at-risk relatives, particularly those beyond the immediate nuclear family, and consider direct outreach models.

Lynch syndrome, caused by germline pathogenic variants in mismatch repair (MMR) genes (MLH1, MSH2, MSH6, PMS2) or deletions in EPCAM, accounts for 2% to 5% of all colorectal cancers. Individuals inheriting these variants face a lifetime colorectal cancer risk as high as 80%, alongside elevated risks for endometrial, ovarian, gastric, urinary tract, and other cancers. Early identification through genetic testing allows for targeted surveillance, such as more frequent colonoscopies and prophylactic hysterectomies, which demonstrably reduces morbidity and mortality.1,2

The process of cascade testing, where relatives of an identified proband are offered genetic testing, is therefore a cornerstone of Lynch syndrome management. It extends the benefits of genetic knowledge beyond the initial patient, allowing at-risk family members to implement preventive strategies. Despite its clear utility, studies consistently show suboptimal uptake of cascade testing. This gap represents a significant public health challenge, as preventable cancers continue to occur in families where the genetic risk is already known.1,2

Understanding the Barriers to Uptake

A systematic review and meta-analysis by Chandler, Ahsan, and Frontera, published in JCO Oncology Practice, synthesized data from 32 studies involving over 15,000 relatives of probands with hereditary cancer predisposition genes, including Lynch syndrome.2 The review aimed to quantify cascade testing uptake and identify factors influencing it. The authors defined cascade testing as germline genetic testing performed on family members after a pathogenic variant was identified in a proband. They included studies that reported uptake rates, defined as the proportion of at-risk relatives who completed genetic testing.2

The meta-analysis found the overall cascade testing uptake rate across all hereditary cancer syndromes to be 35% (95%

CI, 29%-41%). For Lynch syndrome specifically, the uptake was slightly higher but still fell short of ideal, hovering around 40%. This figure represents a substantial proportion of at-risk individuals who are not receiving potentially life-saving information. The studies included in the review spanned various healthcare systems and geographic regions, highlighting the pervasive nature of this challenge.2

Chandler and colleagues identified several factors associated with higher uptake. Direct contact from a healthcare provider, rather than relying solely on the proband to disseminate information, significantly improved testing rates. When a healthcare provider initiated contact with at-risk relatives, uptake was 1.8 times higher (OR 1.8; 95% CI, 1.3-2.5; P=.003). This suggests that passive models of information transfer are insufficient.2

The type of healthcare provider initiating contact also mattered. Genetic counselors or specialized nurses achieved higher uptake rates compared to general practitioners. This is likely due to their specialized knowledge of genetic conditions, their ability to explain complex genetic concepts, and their dedicated time for patient education and support. The meta-analysis also noted that the availability of genetic counseling services, either in-person or via telehealth, correlated with improved uptake.2

Family Dynamics and Referral Pathways

Namey, Horton, and Dudley explored differences in cascade genetic testing among families with hereditary cancer risk in their JAMA Network Open study.1 This retrospective cohort study analyzed data from a large academic medical center's hereditary cancer registry, focusing on 1,847 relatives from 312 families with identified pathogenic variants, including those for Lynch syndrome. The primary outcome was completion of cascade genetic testing.1

The study found that first-degree relatives (parents, siblings, children) of probands were significantly more likely to undergo cascade testing than second-degree relatives (aunts, uncles, grandparents, grandchildren, nieces, nephews). First-degree relatives had a 2.5-fold higher likelihood of testing (OR 2.5; 95% CI, 1.8-3.4; P1

But the proband's characteristics also played a role. Probands who were younger at diagnosis of their cancer or at the time of their own genetic testing were more likely to have relatives undergo cascade testing. This could be due to younger probands having more living relatives, or perhaps being more proactive in family communication. Probands who received genetic counseling themselves also had a higher rate of cascade testing among their relatives, reinforcing the importance of expert guidance.1

The study also highlighted the impact of the initial referral pathway. Relatives referred directly by a genetic counselor or a specialist (e.g., oncologist, gastroenterologist) had higher testing rates compared to those referred by a primary care physician. This is not a criticism of general practice, but rather an indication of the specialized knowledge and dedicated resources available in genetics clinics. The complexity of explaining genetic risk, inheritance patterns, and the implications for surveillance often requires more time and expertise than a typical GP appointment allows.1

The type of pathogenic variant also influenced uptake. Variants with higher penetrance and more severe clinical implications (e.g., MLH1 and MSH2 in Lynch syndrome) were associated with slightly higher cascade testing rates compared to those with lower penetrance (e.g., PMS2). This suggests that the perceived severity of the risk influences a relative's decision to pursue testing.1 For clinicians managing these complex cases, the Oxford Handbook of Oncology can be a valuable quick reference for understanding the nuances of cancer predisposition syndromes.

The Economic Argument for Proactive Testing

Rustgi, Soddano, and Ingram, in their study published in Clinical Gastroenterology and Hepatology, examined the cost-effectiveness of Lynch syndrome identification strategies and their impact on at-risk relatives.3 While not directly measuring uptake, their work provides a strong economic rationale for improving cascade testing. They used a decision-analytic model to compare different strategies for identifying Lynch syndrome in individuals with colorectal cancer and subsequently assessing the cost-effectiveness of cascade testing in their relatives.3

The model demonstrated that universal tumor screening for Lynch syndrome in all colorectal cancer patients, followed by germline genetic testing for those with suspicious results, was the most cost-effective strategy for identifying probands. But the economic benefits extended far beyond the proband. Cascade testing of at-risk relatives, once a proband was identified, was highly cost-effective, and in many scenarios, cost-saving.3

The cost-effectiveness was driven by the significant reduction in cancer incidence and mortality among tested relatives who subsequently underwent enhanced surveillance. For example, the model estimated that for every 100 relatives who underwent cascade testing and were found to carry a pathogenic variant, approximately 15 colorectal cancers and 5 endometrial cancers could be prevented over their lifetime through appropriate surveillance and prophylactic measures. This translates into substantial healthcare cost savings from avoided cancer treatments.3

The study calculated that the incremental cost-effectiveness ratio (ICER) for cascade testing in relatives was well below commonly accepted thresholds for cost-effectiveness, often even showing net savings. This economic argument underscores that the upfront investment in genetic counseling and testing infrastructure for cascade screening is justified by long-term health benefits and reduced healthcare expenditures.3

Addressing the Gaps in Practice

The consistent finding across these studies is that current cascade testing models are not reaching enough at-risk individuals. The reliance on probands to inform and motivate their relatives is a significant limitation. Family communication about genetic risk can be complex, fraught with emotional challenges, and often incomplete. Relatives may not fully grasp the implications, or they may face barriers to accessing testing, such as geographical distance or lack of insurance coverage.1,2

One clear implication is the need for more proactive, direct outreach to at-risk relatives. This could involve dedicated genetic navigators or specialized nurses who work with probands to identify relatives and then directly contact them to offer counseling and testing. Such models, while requiring initial investment, have shown higher uptake rates. Telehealth genetic counseling has also emerged as a viable option to overcome geographical barriers and improve access, particularly for relatives living in remote areas.2

But the open-label design of many studies included in the meta-analysis is an obvious caveat. The lack of blinding in genetic testing studies is inherent, but it means that patient and provider expectations could influence reported uptake rates. Also, the definition of "at-risk relative" varied slightly across studies, which could introduce heterogeneity. Still, the overall trend of suboptimal uptake and the factors influencing it remained consistent across diverse methodologies.2

The trials were not powered to detect differences in very rare Lynch syndrome variants, and that gap matters for comprehensive understanding. The focus on colorectal and endometrial cancer prevention, while appropriate given their prevalence in Lynch syndrome, means that the impact on other associated cancers might be underestimated in some economic models. Future research should explore the effectiveness of different direct outreach strategies in diverse

populations and evaluate their long-term impact on cancer incidence and mortality. The goal remains to ensure that every individual at risk for hereditary cancer receives the information and interventions necessary to prevent disease.1,3

CLINICAL IMPLICATIONS

The data on cascade testing for Lynch syndrome is clear: we are not doing enough. Relying on probands to inform their families is a passive approach that leaves too many at-risk relatives unaware and untested. Clinicians must shift to a more proactive model, actively identifying and engaging with all first- and second-degree relatives. The economic arguments for this are compelling, showing that upfront investment in genetic services pays dividends in prevented cancers and reduced treatment costs.

The disparity in testing rates between first- and second-degree relatives highlights a critical failure point. Genetic counselors and specialized nurses are demonstrably more effective in facilitating testing than general practitioners alone. This suggests a need for enhanced referral pathways and better integration of genetic services into routine oncology and gastroenterology practice. GPs should be empowered to identify potential Lynch syndrome cases and refer appropriately, but the heavy lifting of family outreach often requires dedicated genetic expertise.

For industry, this represents an opportunity to develop and implement scalable solutions for direct relative outreach. Telehealth platforms and digital tools could streamline the process of identifying, contacting, and counseling at-risk individuals, especially in geographically dispersed families. The current fragmented approach is inefficient and costly in human terms, leading to preventable cancers.

The goal is to ensure that every individual with a pathogenic variant in a cancer predisposition gene, and their at-risk relatives, receives the information and support needed to make informed decisions about their health. The current uptake rates are a stark reminder that significant work remains to be done to translate genetic knowledge into widespread clinical benefit.

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