

The explosion of hereditary cancer knowledge: benefiting from a family information service

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Both oncology professionals and the public at large are becoming more aware of hereditary cancer syndromes and the importance of genetic counseling and other cancer-prevention strategies in families at risk. A family information service (FIS) is a cost-effective and professionally satisfying means of communicating both good and bad news to a family carrying a deleterious, cancer-causing germline mutation. Often these mutations come to light through observation of the pattern of cancer in an extended family, based on clinical, pathologic, molecular genetic, and genealogic information gathered from the family. The FIS serves as a tool for informing not only immediate members of the family who might be affected but also distant relatives who may be totally unaware of their risk or even that they are part of the family. Participation in an FIS can be a way for cancer-prone families to discuss issues that affect them all in a highly effective, structured, and supportive manner—and that may even prove to be lifesaving. This article describes the mechanics of setting up an FIS and describes some of the rewarding experiences the authors have had conducting these sessions over the past several decades.

Despite the recent groundswell of knowledge about hereditary forms of cancer, its translation into the clinical setting has been problematic. To cite just one example, a comprehensive history of cancer in a family, often the linchpin of this effort, has been insufficiently recorded in many patients' medical records, thereby compromising its clinical significance.¹ A recent survey of American Society of Clinical Oncology (ASCO) members suggests that

physicians are increasingly becoming aware of the importance of recognizing hereditary cancer syndromes and their potential in cancer control.² In turn, knowledge about advances in molecular genetics, particularly the proliferation of discoveries of cancer-related germline mutations, has been increasing so rapidly as to outpace their comprehension by practicing physicians at virtually every clinical level. However, there is a high level of agreement among ASCO members that they need more education about these matters to integrate this knowledge into more effective hereditary cancer prevention and control procedures.² Barriers along the way to these objectives are not just a physician problem; they also involve families who must participate actively in this awareness process and, once diagnosed with a cancer-causing hereditary syndrome, comply with surveillance and management recommendations, if cancer control is to achieve success.

How can this mass of emerging genetic information be effectively marshaled in the interest of maximal benefit to members of cancer-prone families? One novel approach is the family informa-

KEY POINTS

A family information service (FIS) is a cost-effective and professionally satisfying means of communicating both good and bad news to cancer-prone families.

Often a deleterious germline mutation comes to light only by observing a pattern of cancers running through the generations of a family.

The FIS is highly cost-effective because it allows knowledgeable physicians, nurses, and genetic counselors to have personal contact with a large number of at-risk family members all at the same time.

The information sharing that typifies an FIS is not only emotionally and psychologically satisfying but also can be lifesaving.

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tion service (FIS),³ the primary focus of this article. But for the cancer-prevention message of an FIS to be effectively implemented, the family needs to be identified, its clinical features recognized and understood, and full compliance with surveillance and management recommendations must take place.³

Why is a family history important?

A hereditary cancer syndrome diagnosis at the outset involves compiling a comprehensive family history. Medical and pathologic verification of each case of cancer in the family, although extremely valuable and worthy of investigation, may, admittedly, prove difficult to obtain in the usual clinical practice setting. Nevertheless, the search for it, wherever possible, may prove to be tremendously rewarding.

It is mandatory to meticulously record cancer of *all* anatomic sites, given the fact that certain hereditary cancer syndromes may be identifiable only by the *pattern* of multiple primary cancers in at-risk individuals. Cancer-causing germline mutations in carriers are the *sine qua non* for diagnosis. For example, the MEN2A/B endocrine neoplasia syndromes show a striking confluence of medullary thyroid carcinoma with pheochromocytoma. The *RET* proto-oncogene mutation is diagnostic.

Phenotypic variation abounds

Familial adenomatous polyposis (FAP) is characterized by multiple colonic adenomas giving rise to early-onset colorectal cancer (CRC); however, FAP patients also have an inordinately high risk for gastric cancer (particularly among FAP families in Asia), as well as carcinomas of the duodenum and pancreas, brain tumors (medulloblastomas) in the Turcot's syndrome variant, and ominous desmoid tumors. The *APC* mutation is identified in about 80% of FAP cases. This mutation will be of particular diagnostic aid in the clinical variant of classic FAP, aptly known as

attenuated FAP due to a paucity of colonic adenomas and a generally later age of onset.⁴ About 10% of patients with a perhaps milder form of adenomatous polyposis carry the *MYH* mutation.

Although CRC predominates in Lynch syndrome, a litany of extracolonic cancers also may occur, including gastric cancer (again, particularly in Asian families); carcinomas of the endometrium (second only to CRC in frequency in this syndrome), ovaries, duodenum, and pancreas; and cancers of the upper uroepithelial tract. In the Muir-Torre variant of Lynch syndrome, we also see cutaneous lesions, namely, sebaceous adenomas, carcinomas, and multiple keratoacanthomas. Mutation of a mismatch repair gene, most commonly *MSH2*, *MLH1*, or *MSH6*, is diagnostic.

Familial atypical multiple mole melanoma (FAMMM) syndrome, also called dysplastic nevus syndrome, displays a pattern of multiple dysplastic nevi in association with cutaneous and, rarely (but nevertheless integral to the FAMMM phenotype), intraocular malignant melanoma. Pancreatic carcinoma and sarcoma may also occur in carriers of *CDKN2A* (p16) mutations, the most common cause of FAMMM.⁵

Diagnostic clinical signs may abound in certain hereditary cancer syndromes (eg, multiple colonic adenomas in FAP, perioral pigmentations Peutz-Jeghers syndrome, and multiple atypical nevi in FAMMM syndrome). These findings will be useful to the physician who understands the natural history of these hereditary cancer syndromes. Particular attention must be given to the variation in gene penetrance and expressivity of phenotype, which, in turn, may be confounders to their diagnosis.

A striking example is the paucity of colonic adenomas in the attenuated form of FAP. The FAMMM syndrome is no different. Specifically, occasional patients with a *CDKN2A* mutation may have only a few atypical nevi, thereby posing a diagnostic challenge. Conversely, some FAMMM families may show an extraordinary excess of pancreatic cancer

among carriers of this mutation.⁵ This variable expressivity of phenotype only tends to confound a hereditary cancer syndrome diagnosis. Nevertheless, the gestalt of clinical, pathologic, molecular genetic, and genealogic information gathered from a family can be utilized to great advantage in what we refer to as "pattern recognition," particularly when a deleterious mutation known to predispose to the syndrome is present.

Informing the family

Once a hereditary cancer syndrome is confirmed in a family, this information may not reach all at-risk family members. This shortfall becomes a severe problem when many members of a hereditary cancer syndrome family are unaware of the fact that they are even part of the family—they may be at an inordinately high cancer risk and never know it. Therein, they will never know how the presence or absence of a deleterious germline, cancer-causing mutation may significantly alter their lifetime cancer destiny. For example, if they harbor the deleterious mutation, they may benefit immensely through available cancer-control practices; contrariwise, should they test negative, they will then revert to expectations of cancer risk based upon its occurrence in the general population. However, even when given the "good news" of a negative finding, these family members still require counseling so that they can fully understand the meaning of "freedom" from the enormous lifetime risk that their mutation-positive relatives will encounter. Not infrequently, they may harbor survivor guilt, expressing concerns such as "Why was I spared when my sibling received the news about having the harmful mutation?"

It is in these and countless other settings that their participation in the FIS can be a way for cancer-prone families to discuss these issues in a highly effective and informative manner. The logistics of the FIS enables as many family members as may wish to assemble at a mutually convenient

geographic site to share collectively in information that may be entirely new to them about their “family disease”—and it could prove to be lifesaving.

What constitutes an FIS?

An FIS is a simple yet highly targeted and structured program (Figure 1) designed to educate families about their hereditary cancer disorder.^{3,6} Ideally, it involves a knowledgeable physician and paramedical professionals (eg, genetic counselor, registered nurse) who, working together, can intensively educate a large number of family members at a single setting. An added benefit will take place when a cancer-causing germline mutation has been identified in the family. Therein, consenting relatives will have the opportunity to provide a sample of blood, buccal mucosa, or saliva for future testing of their DNA in a commercial or research laboratory.

Frequently, family members will help with the planning details required for the success of the FIS. Thus, once these key family members are sufficiently knowledgeable about all ramifications of “their” hereditary disorder, they can assist in contacting their relatives, telling them what the FIS is all about, scheduling the date, and selecting a geographic site that will be convenient to as many members of the family as possible. Once these family volunteers realize the desire and commitment of the genetic team members to provide this type of help to the family, their active participation in the project, may, in our experience, know no bounds!

Why is an FIS important?

High-risk family members, as mentioned, may be completely unaware of their membership in a cancer-prone family. The inclusion of the records of as many of these relatives as possible may be of benefit both to them and to those family members who are already aware of the family’s hereditary cancer syndrome. A major benefit is that after a deleterious mutation has been identified in a family, other high-risk family mem-

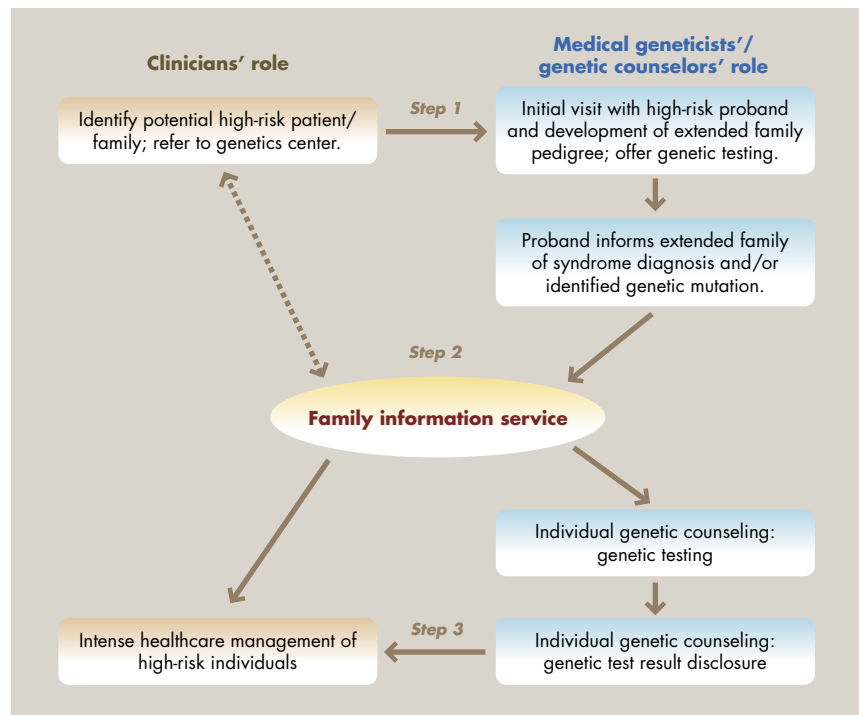


FIGURE 1 Algorithm showing the steps involved in organizing and providing a family information service.

bers can undergo DNA testing for that one specific mutation at a cost that is markedly lower than that spent on initially identifying the mutation. Another benefit is the fact that not every family member needs to be tested to learn his or her mutation carrier status. This was clearly evident in an observational study of 75 hereditary breast-ovarian cancer (HBOC) and 47 Lynch syndrome families.⁷ Of the 10,910 individuals in the cohort, inclusion in their family’s study changed the mutation carrier risk status of 2,906 family members. That is, they were more certain that they either were or were not a mutation carrier after the study’s completion than they had been previous to it. But perhaps the most striking result was that 60% of those who had a risk status change were not tested themselves; rather, their carrier risk status changed because of a relative’s test result. This is of crucial importance, given the fact that carrier risk status significantly affects cancer-prevention recommendations, most commonly *reducing* their burden.

Clearly, first-degree relatives of a hereditary cancer syndrome-affected individual and/or germline mutation carrier may attain clinical benefit through knowing that they have an enormous lifetime risk for cancer. Knowledge that a germline mutation has been identified in the kindred and that it could determine with certainty their lifelong cancer risk status, when communicated effectively, may be exceedingly rewarding, particularly when knowing that regular screening with early detection could save their lives. However, this very issue is not without a potentially high emotional burden. Is this individual emotionally capable of undergoing DNA testing? Is there fear of insurance and/or employment discrimination or concern about possible rejection by offspring and/or other loved ones if the mutation test is positive?

In an FIS setting, a freewheeling discussion about these and other concerns may be facilitated. Such a catharsis may yield psychological benefits, particularly when individuals are able to discuss

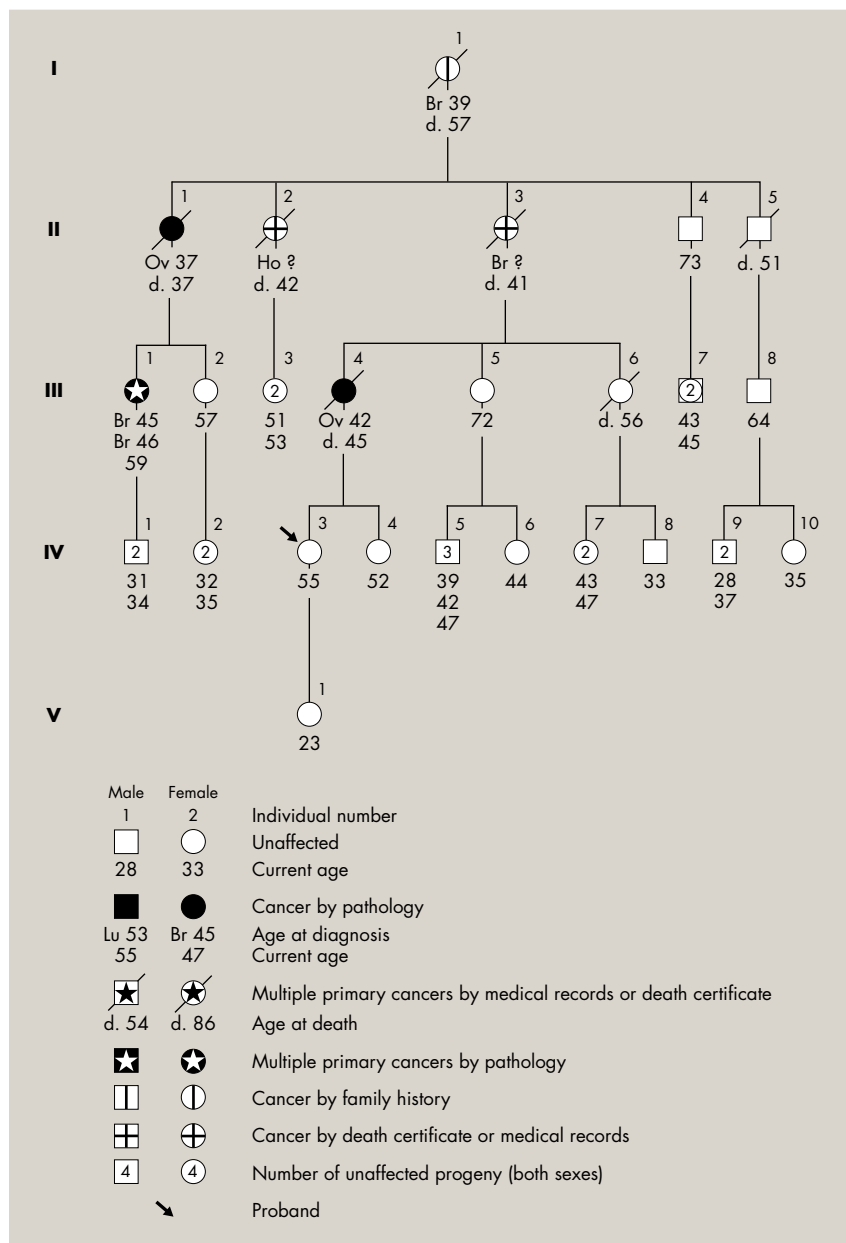


FIGURE 2 Pedigree of family A. Br = breast cancer; Ho = Hodgkin’s lymphoma; Ov = ovarian cancer. Illustration based on a pedigree constructed by Tami Richardson-Nelson, BGS.

these issues more freely among their relatives since “We’re all in this together.” The physician can seize the opportunity to elicit such a dialogue, which, in our experience, may help to lessen these emotional burdens.

Low- as well as high-risk family members are provided a unique opportunity by an FIS to ask questions about those salient issues that pertain to their hereditary cancer risk and

thereby benefit collectively from new genetic knowledge. This information becomes particularly valuable when it is described in a manner that they can fully understand, particularly in terms of what it means, both clinically and genetically, to be a member of a hereditary cancer-prone family.

The structure and logistics of the FIS (Figure 1) will provide an opportunity for the physician and the team’s

paramedical personnel to listen attentively to family members’ questions, recognize their emotional needs, and then explain more fully how these concerns can be effectively mollified. Surveillance and management options, as well as the significance of DNA testing, can be explained in a highly practical manner. Family members may then assess more fully their cancer risk concerns in more accurate and realistic terms with help from each other and the FIS team. The quality of the emotional support provided by family members in this group therapy-like setting is often equal to or even superior to that which may take place during a one-on-one patient/physician counseling session; it may actually become one of the major benefits of an FIS. Indeed, once shared information about the disease emerges, it will often stimulate the recollection of greater detail about their family history. In those families that have problems communicating with each other, the facilitator will need to be aware of this communication barrier and be prepared to deal with it during the course of the FIS meeting.

Clinical vignettes

Just how well the FIS concept works is illustrated by these brief clinical vignettes.

Family A (Figure 2). This family’s proband (IV-3) had known for 10 years that her DNA test result was available, before she attended our FIS. She had decided against receiving her result at that time, stating that she wasn’t prepared psychologically to receive a potentially positive mutation result. At age 44, she decided to have a prophylactic oophorectomy in the absence of knowing her mutation carrier status.

A decade after the FIS, knowing that her 23-year-old daughter (V-1) could benefit from information for her own health management, the patient decided to receive her result. She was found to be positive for the *BRCA1* mutation.

Family B (Figure 3). When the pro-

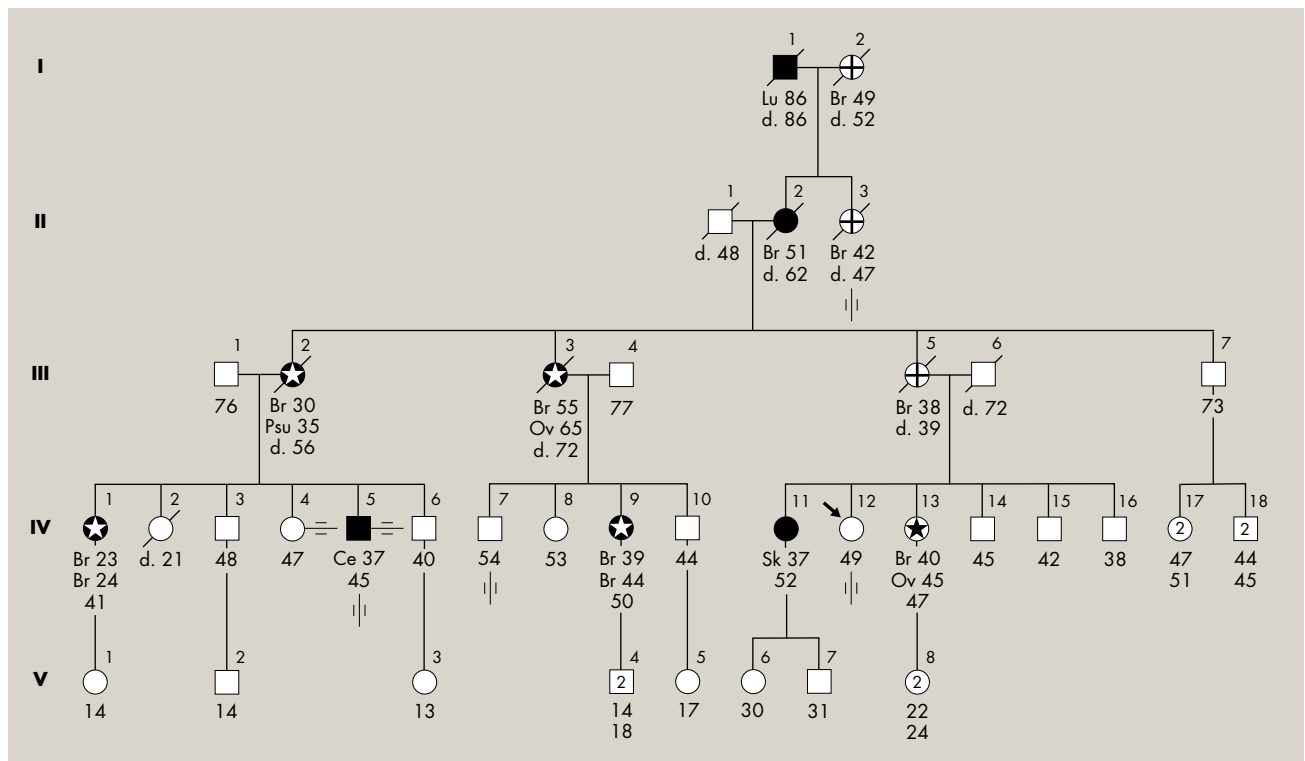


FIGURE 3 Pedigree of family B. See Figure 2 for an explanation of the pedigree symbols. Br = breast cancer; Ce = cecum colon cancer; Lu = lung cancer; Ov = ovarian cancer; Psu = primary site unknown; Sk = skin cancer. Illustration based on a pedigree constructed by Tami Richardson-Nelson, BGS.

band (IV-12) of this family was 13 years old, her mother (III-5) developed breast cancer and died from the disease. The proband then moved to her aunt's home, where a cousin (IV-9) and then her aunt (III-3) were each diagnosed with both breast and ovarian cancers. The occurrences of these cancers caused the proband to develop a severe cancer phobia and a constant sense of doom. She proceeded to live a deviant lifestyle of unhealthy relationships, drug and alcohol use, and frequent moves.

At age 44, she agreed to be DNA tested for the deleterious *BRCA1* mutation. She subsequently attended an FIS and decided to receive her genetic test result, which was negative for the *BRCA1* mutation. She promptly stated, "I just wasted half of my life thinking I was going to die young from cancer. Now I have hope for my future."

Family C. One of our largest FIS experiences involved an HBOC family wherein the *BRCA1* germline mu-

tation was identified.³ The local family physicians were intensely interested, as evidenced by their attendance at a dinner with us the evening before the FIS. We were then able to have an in-depth discussion with them about the genetic and clinical management of HBOC. This experience was rewarding for both these physicians and ourselves.

We had begun the study of this family about a decade prior to this session. In all, 89 members of this large family of more than 600 members attended the FIS. The efforts of the family volunteers during their preparation for this all-day cancer educational program had led to the identification of more than 100 family members who heretofore had had absolutely no knowledge of the hereditary pattern of cancer in their family.³ Following the 3-hour group educational session in the morning, the rest of the day was spent in personal discussions with those family members who wished to receive additional education

and to focus on knowledge relevant to interpretation of their DNA test results and/or consideration of their wish to be tested. Blood was then drawn from consenting individuals.

But is an FIS effective?

One may ask the most appropriate question, "Is this intellectual and psychological discourse in an FIS setting effective?" The answer from our perspective is a resounding "Yes!" Throughout our experience of conducting more than 100 such FIS sessions during the past several decades, both nationally and internationally, we have been impressed with how frequently patients tell us that, in essence, "This was the *first* time in my life that a physician told me face-to-face what could kill me, but in the same breath told me how I could help to reduce my cancer risk through appropriate screening and management strategies." The very presence of a physician discussing these matters in the fam-

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Communication of risk in hereditary cancer families—the family information service

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“... in the beginning of the malady it is easy to cure but difficult to detect, but in the course of time, not having been either detected or treated in the beginning, it becomes easy to detect but difficult to cure.”

— Niccolò Machiavelli, *The Prince*

Over the past 2 decades, our knowledge of hereditary cancer syndromes has expanded rapidly. As described by Lynch and colleagues, identification of patients at risk for a hereditary cancer syndrome, their subsequent referral to a genetics center for syndrome identification and possible testing, and management of cancer risk have become an integral part of oncology practice. Through cancer genetic counseling, a hereditary cancer syndrome can be identified by careful documentation of the family medical history and medical records review. In many of these families, a cancer susceptibility gene mutation is identified. The clinician's ultimate goal is early cancer detection and possible cancer prevention through careful medical management of the hereditary cancer risk for the proband and at-risk family members.

Once a hereditary cancer syndrome is identified, the cancer genetics team communicates relevant information about cancer risk with the proband. The team will also encourage the proband to share with his or her relatives information about the syndrome, the family members' at-risk status, and the potential associated cancer risks. Often, the genetics team will provide a letter describing relevant information and recommend that the proband

share it with at-risk relatives.

Various groups have studied the communication of genetic test results within families. Although many probands disclose their test results, especially to close relatives, there is evidence that relatives often do not understand the meaning of the test result or that they are at higher risk for cancer. Additionally, there is a need for genetic counseling strategies that address communication with more distant relatives.¹ A study by Mellon et al² supports the inclusion of family members in addressing inherited cancer risk information. Wagner Costalas et al³ concluded that other problems with risk communication include the observation that probands in hereditary breast-ovarian cancer (HBOC) families more often shared their results with their female relatives than with their male relatives. Furthermore, probands with positive genetic test results were more likely to experience difficulty and distress communicating their test results to family members.

Overcoming barriers to risk communication

The family information service (FIS) concept that Lynch et al wrote about in the accompanying article overcomes these barriers to risk communication. I was fortunate to help coordinate one FIS conducted by Dr. Lynch and the Creighton University team for the

large family with HBOC syndrome described in their article. As a genetic counselor, I had the opportunity to work closely with many members of this large family. One member of the Creighton University team (Carrie Snyder), three highly motivated members of this large family, a genetic counseling student, and I organized this HBOC syndrome FIS. This family event was described in a letter, and the three key family members took the responsibility for identifying appropriate family members and sending this invitation to almost every at-risk adult in the family. The family members also received information packets from Creighton University. With the commitment of Dr. Lynch's team, in conjunction with the efforts of key family members, more than 100 family members attended this greatly successful FIS. At the FIS, they learned about HBOC, the familial cancer susceptibility mutation (*BRCA*) responsible for it, and the associated cancer risk, as well as their options for testing for the familial mutation and management of cancer risk for mutation carriers and those who declined genetic testing.

Many participants expressed satisfaction with the FIS and their increased understanding of the hereditary cancer risk information shared by the team. Receiving information

from a trusted experienced clinician in a supportive group setting made this information less threatening.

By involving at least one member with cancer genetics expertise, the FIS team can provide information about cancer risk management to many at-risk family members effectively. As described by Lynch et al, an FIS has the potential to invoke strong emotions. These emotions can also be powerful motivators for adherence to medical management recommendations. At this FIS, the at-risk relatives heard the clear message that early management of cancer risk is important. According to D. Bowen (personal communication, 2006), knowing the risk, charting a path of action, and having support for that path are the keys to driving a change in health behavior.

Personal experience

I subsequently coordinated an FIS for another motivated HBOC family and had approximately 30 partici-

pants. In a pre- and post-survey (unpublished), the participants were asked to rate their knowledge of the familial *BRCA* mutation in their family on a scale of 1–10 (with 10 being the highest level of knowledge). The average score before the FIS was 3; after the meeting, it was 8. At the FIS, individuals were given written resources and were encouraged to discuss the risk of HBOC with their primary care physician to develop an individualized cancer surveillance plan. The at-risk relatives were asked to contact our genetics clinic if they wished to pursue a cancer genetics consultation individually and to discuss in more detail their options to pursue testing. Since that meeting less than 1 year ago, many at-risk family members have been in touch with a genetic counselor to obtain further information.

Lynch's team report their experience conducting hundreds of these FIS sessions as a resounding success. With my limited FIS experience, I echo their conclusion that when led by at least one

member with expertise in cancer genetics and one individual who knows the family well, an FIS is the most effective method of providing important hereditary cancer-risk information to the largest number of at-risk relatives in a supportive setting. It is important to continue gathering data to validate these findings.

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ily-group setting, with frequent back-and-forth verbal and body-language exchanges with high cancer-risk family members, significantly helps to elicit strong psychological support.

Conclusion

The FIS will often accelerate progress on the patients' learning curve about the "family cancer disease." An FIS is highly cost-effective in that it allows knowledgeable physicians and paramedical staff to have personal contact with a large number of at-risk family members, all of whom can share in what will be, perhaps, the most important educational experience of their lives.

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