Cancer Predisposition Syndromes 101: A Case History and Review of the Challenges

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Case History

In April of your third year of medical school, you are starting an elective in Pediatric Oncology. You are asked to see a 10-year-old boy who just completed chemotherapy for a localized osteosarcoma of his distal femur. You take a few minutes to review his medical chart and discover that this child's mother is currently being treated for a second breast cancer lesion, and she is only 40 years old. You then notice a report of a genetic test done two weeks ago showing a mutation in the *TP53* gene. You search the meaning of a *TP53* mutation on the Internet and find out that it is associated with Li-Fraumeni syndrome (LFS). The resident working with you explains that LFS is a cancer predisposition syndrome (CPS), but then gets paged away. Many questions flow through your curious mind. What is a CPS? What should I worry about in LFS? How do I best manage this patient? Motivated, you decide to take a few more minutes to read and better plan out the upcoming medical encounter with the child.

What is a cancer predisposition syndrome (CPS)?

When a child or adult is diagnosed with a cancer, among the first questions that arise in the patient's or parents' mind are what caused this tumour and are their family members at increased risk of cancer? These concerns can rapidly become anxiety provoking for a patient who already has so much to worry about. Although a combination of genetic and environmental factors is the most likely explanation for tumorigenesis,[1,2] a precise etiology cannot be identified in the majority of cases. In adults, environmental factors including tobacco, excessive sun exposure, gamma-irradiation, and alcohol intake have been linked to the development of various maligancies.[1,3,4] Viruses, such as the human papilloma virus (HPV)[5] and the Epstein-Barr virus (EBV),[6] have also been linked to specific cancers. In contrast, most children have not had significant long-term exposures to such environmental factors yet they can still develop malignancies. In this age group, cancers may arise as a result of genetic and epigenetic alterations at a cellular level during the normal processes of growth and development.[7]

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A smaller proportion of cancers are hereditary in nature, implying that a genetic alteration has been passed on to a child from a parent or that a new mutation has occurred in the germinal cells prior to fertilization (*de novo* mutation). When these processes arise, all the child's cells carry this genetic change. This is the definition of a germline mutation, in contrast to a somatic mutation which is acquired during one's lifetime.[8,9] A CPS results from a germline genetic alteration leading to an increased risk of tumour development over one's lifetime. Genetic mutations can affect cellular function in a variety of ways that will lead to abnormal proliferation, survival, and apoptosis or DNA breakage and repair mechanisms.[8] Cancer susceptibility genes are usually categorized as one of two subtypes: a tumour suppressor gene or an oncogene. A tumour suppressor gene normally acts by inhibiting cell proliferation and tumour development. Examples include *RB1*, *TP53*, and *ATM*, associated with retinoblastoma predisposition, LFS, and ataxia-telangiectasia respectively. In contrast, an oncogene drives abnormal cell proliferation and protein expression. For example, mutations in the *RET* oncogene leads to multiple endocrine neoplasia syndrome type 2. Each CPS is thought to be driven by pathogenic variants in a tumour suppressor or oncogene; however, a complex array of germline and somatic alterations of other genes is likely responsible not only for the variable spectrum of tumours associated with each CPS, but also the age of onset, disease penetrance, and probably the biological aggressiveness of these tumours.

How common are inherited cancer syndromes?

An underlying CPS is thought to be present in at least 10% of patients diagnosed with a malignancy, with a higher prevalence in children.[10,11,12] This estimate is increasing as we continue to discover the genetic background of cancer. According to a recent publication by Rahman,[9] approximately 114 cancer predisposition genes have been discovered in the past 30 years.[8] Several recent studies using next generation sequencing platforms report a germline pathogenic variant in a known "cancer gene" in 8.5-10% of children whose tumours were sequenced for the purpose of identifying molecular targets for novel drug therapies.[13,14,15] A more complex genetic etiology is suspected in approximately 45% of other

Table 1. Cancer Predisposition Syndrome Types with Associated Cancers and Causal Genes[8,11,22,23,24]

Cancer Susceptibility Syndrome	Related Cancer Types	Affected Genes (chromosomal locations)
Ataxia-telangiectasia syndrome	Leukemia, lymphoma (majority T cell)	*ATM* (11q22)
Beckwith-Wiedemann syndrome	Wilms tumour, hepatoblastoma, adrenocortical carcinoma, rhabdomyosarcoma, neuroblastoma	*CDKN1*, 11p15 methylation defects/uniparental disomy, *IGF2*
Biallelic mismatch repair deficiency	High grade glioma, leukemia, lymphoma, colorectal cancer	*MSH2* (2p21), *MSH6* (2p16), *PMS2* (7p22), *MLH1* (3p21)
Birtt-Hogg-Dubé syndrome	Renal cell carcinoma	*FLCN* (17p11)
Bloom syndrome	Leukemia, myelodysplastic syndrome, lymphoma, epithelial cancers, hepatocellular carcinoma, sarcoma, brain tumours, Wilms tumour	*BLM* (15q26)
Breast/ovarian cancer syndrome	Breast cancer, ovarian cancer	*BRCA1* (17q21), *BRCA2* (13q12)
Costello syndrome	Rhabdomyosarcoma	*HRAS* (11p15)
Cowden syndrome (PTEN hamartoma syndrome)	Cerebellar dysplastic gangliogliomа, breast cancer, endometrial cancer, thyroid cancer, hamartomas of the central nervous system, eyes, gastro-intestinal/genito-urinary tracts and bone	*PTEN* (10q23)
DICER1 syndrome	Pleuropulmonary blastoma, cystic nephroma, pineoblastoma, pituitary blastoma, ovarian sex-cord stromal tumour, ovarian Sertoli-Leydig cell tumour, multinodular goiter, rhabdomyosarcoma	*DICER1* (14q32)
Familial Wilms Tumour syndrome (WAGR, Denys-Drash, Frasier syndromes)	Wilms tumour	*WT1* (11p13)
Familial adenomatous polyposis - Turcot syndrome - Gardner syndrome	Colorectal carcinoma, gastric carcinoma, hepatoblastoma, thyroid tumour, desmoid tumour, aggressive fibromatosis, medulloblastoma, astrocytoma	*APC* (5q21)
Familial neuroblastoma	Neuroblastoma	*ALK* (2p23), *PHOX2B* (4p12)
Fanconi anemia	Myeloid leukemia, myelodysplastic syndrome, medulloblastoma, primitive neuroectodermal tumour, Wilms tumour, squamous cell carcinoma, epithelial cancers, genitourinary tract tumours, breast cancer	*FANCA* (16q24), *FANCB* (Xp22), *FANCC* (9q22), *BRCA2* (13q12), *BRIP1* (17q22), *FANCD2* (3p26) *FANCE* (6p21), *FANCF* (11p15), *FANCG* (9p13) *FANCI* (15q26), *FANCL* (2p16), *FANCM* (14q21) *PALB2* (16p12), *RAD51C* (17q22), *SLX4* (16p13)
Gorlin syndrome (nevoid basal cell carcinoma syndrome)	Basal cell carcinoma, medulloblastoma, cardiac and ovarian fibroma	*PTCH1* (9q22), *SUFU* (10q24)
Hereditary leiomyomatosis and renal cell cancer syndrome	Leiomyoma, renal cell cancer	*FH* (1q42)
Hereditary retinoblastoma	Retinoblastoma, pineoblastoma	*RB1* (13q14)
Juvenile polyposis syndrome	Hamartomatous polyps of the gastro-intestinal tract, colorectal cancer, gastric cancer	*SMAD4* (18q21), *BMPR1A* (10q22)
Li-Fraumeni syndrome	Sarcoma, brain tumors, leukemia, breast cancer, choroid plexus carcinoma, adrenocortical carcinoma	*TP53* (17p13), *CHK2* (22q12)
Lynch syndrome (HNPCC)	Colorectal cancer, endometrial cancer, ovarian cancer, urinary tract carcinoma	*MSH2* (2p21), *MSH6* (2p16), *PMS2* (7p22), *MLH1* (3p21)
Multiple endocrine neoplasia type 1 (MEN 1)	Pituitary tumor, parathyroid tumor, entero-pancreatic tumours (pancreatic islet cell tumor, gastrinoma, insulinoma)	*MEN1* (11q13)
Multiple endocrine neoplasia type 2 (MEN 2)	Medullary thyroid carcinoma, pheochromocytoma, paraganglioma, parathyroid hyperplasia	*RET* (10q11)
Neurofibromatosis type 1 (NF1)	Optic pathway glioma, neurofibroma, malignant peripheral nerve sheath tumor, leukemia, high grade gliomas, neuroblastoma	*NF1* (17q11)
Neurofibromatosis type 2 (NF2)	Meningioma, vestibular schwannoma, ependymoma, neurofibroma	*NF2* (22q12)
Nigmegen Breakage syndrome	Leukemia, lymphoma, medulloblastoma, glioma, rhabdomyosarcoma	*NBS1* (8q21)
Peutz-jeghers syndrome	Intestinal tumours (gastric and colon), pancreatic cancers, gonadal tumors, breast cancers	*LKB1* or *STK11* (19p13)
Hereditary pheochromocytoma/paraganglioma	Pheochromocytoma, paraganglioma	*SDHA* (5p15), *SDHB* (1p36), *SDHC* (1q23), *SDHD* (11q23), *SDHAF2* (11q12), *TMEM127* (2q11), *MAX* (14q23)
Rhabdoid predisposition syndrome	Rhabdoid tumors, schwannomatosis	*SMARCB1* (22q11), *SMARCA4* (19p13)
Rothmund-Thomson syndrome	Osteosarcoma, skin tumors	*RECQL4* (8q24)
Rubinstein-Taybi syndrome	Medulloblastoma, peripheral nerve sheath tumor, leukemia, neuroblastoma, pilomatrixoma, rhabdomyosarcoma, osteosarcoma	*CREBBP* (16p13)
Simpson-Golabi-Behmel syndrome	Wilms tumor, hepatoblastoma	*GPC3* (Xq26)
Sotos syndrome	Sacrococcygeal teratoma, neuroblastoma, Wilms tumor, leukemia, lymphoma	*NSD1* (5q35)
Tuberous sclerosis	Subependymal giant cell astrocytoma, hamartomas, cortical tubers, renal and extrarenal angiomyolipoma, renal cell carcinoma, cardiac rhabdomyoma	*TSC1* (9q34), *TSC2* (16p13)
Von Hippel Lindau	Retinal and cerebellar hemangioblastoma, renal cell carcinoma, pheochromocytoma, endolymphatic sac tumor	*VHL* (3p25)
Werner syndrome	Bone and soft tissue sarcoma, melanoma, thyroid carcinoma, meningioma, leukemia	*WRN* (8p11)
Xeroderma pigmentosum	Skin cancers	*XPA* (9q22), *ERCC3* (2q21), *XPC* (3p25), *ERCC2* (19q13), *DDP2* (11p11), *ERCC4* (16p13)

patients in these cohorts based on their (or their families) clinical features. In addition to the ongoing identification of novel cancer predisposition genes, other heritable cancer syndromes such as DICER1 syndrome,[16,17] biallelic mismatch repair deficiency,[18,19] and the SDH-TCA cycle syndromes[20,21] continue to be more effectively recognized by the clinical oncology community. Many of the best described CPSs with their respective tumour spectrum and associated genes are presented in Table 1.

And specifically, what is Li-Fraumeni syndrome (LFS)?

LFS is caused by alterations in the *TP53* gene located on chromosome 17p13.1. Several thousand families have been reported worldwide and the population carrier rate is thought to be approximately 1 in 5,000 births (although some estimates place this rate as high as 1:2000 births), making LFS one of the most commonly known inherited cancer syndromes.[10] *TP53*, often called "the guardian of the genome," mediates cell cycle arrest, DNA repair and apoptosis, and several other biological processes through its influence on the expression of a variety of target genes.[25] In simplified terms, p53 detects and assesses the severity of DNA damage. If the damage is deemed repairable, p53 will initiate a complex DNA-repair activation pathway. If the damage is deemed irreparable, p53 will mediate cell cycle arrest and apoptosis. Mutant p53 is unable to exert these functions, making cells more likely to evade cell cycle arrest and apoptosis to eventually become transformed and tumorigenic. In LFS patients, *TP53* is mutated in the germline (either inherited or *de novo*). Missense mutations account for the majority of these mutations, leading to altered protein expression.[26] The classic tumour spectrum in LFS includes bone and soft-tissue sarcomas, brain tumours, pre-menopausal breast cancer, adrenocortical carcinoma, and leukemia.[27] A wide spectrum of other tumour types have also been reported in these patients.[28] LFS is a highly penetrant disease with the lifetime risk of developing cancer being 75% in men and 93% in women.[10] This higher prevalence in women is partially, though not entirely, due to the excess risk of breast cancers. Half of patients with LFS will develop their first tumour by age 30 and approximately one-third of these cancer survivors will develop multiple primary cancers over their lifetimes.[29]

How can I suspect LFS or any other CPS?

A variety of features in the patient's personal and family history can lead to a higher suspicion of a CPS. Associated dysmorphic features, congenital abnormalities, or an abnormal growth pattern are clues to an underlying germline genetic mutation.[11,22] However, in many situations, identifying inherited cancers is challenging due to the fact that mutations in cancer predisposing genes do not necessarily result in a recognizable clinical phenotype.[22] Occasionally, the tumour itself can be a clue. The presence of more than one primary cancer or bilateral and multifocal tumours in a patient can hint towards a causal germline mutation.[11] An adult-onset cancer occurring at a strikingly young age should also arouse suspicion.[30,31] An example of this might be a colorectal cancer occurring in a 15 year old with familial adenomatous polyposis or biallelic mismatch repair deficiency.

Additionally, the importance of taking a thorough family history cannot be stressed enough. Parental ethnicity and history of consanguinity can hint towards certain autosomal recessive inherited syndromes.[22] The findings of a close relative with multiple cancers, a cancer in the pediatric age range, or the finding of multiple relatives with the same tumour type can heighten the likelihood for a cancer susceptibility syndrome.[11,31,32] Family history is not static; therefore, regularly updating the family history is essential. On the other hand, a common challenge is that patients often lack a positive family history, often because of a small family size, the malignancy has arisen due to a recessive or de novo germline mutation, or because family members are not aware of their relatives' health history.[22,33]

Independent of the personal or family history, certain tumour types such as a malignant rhabdoid tumour, pheochromocytoma, or adrenocortical carcinoma are highly associated with inherited cancer syndromes.[12,34] Occasionally, specific characteristics of the tumour histology can also suggest a diagnosis of a CPS. For example, anaplastic features in rhabdomyosarcoma and desmoplastic histology in medulloblastoma are associated with LFS and Gorlin syndrome respectively.[35,36] For all the reasons noted above, a geneticist and genetic counsellor are essential allies in the diagnostic process of CPSs.

Diagnostic criteria exist for a variety of inherited cancer syndromes including LFS, neurofibromatosis types 1 and 2, PTEN-hamartoma syndrome, von Hippel Lindau syndrome (VHL), and many others. Specific to LFS, three sets of diagnostic criteria exist: the Classic LFS-, the Chompret- and the *LF*-like syndrome criteria. The sensitivity and specificity of the Chompret criteria are 82% and 58% respectively, making it perhaps the most rigorous definition to justify *TP53* mutation testing.[10] The Chompret and Classic Li-Fraumeni criteria are presented in Table 2.

Table 2. Chompret and Classic LFS criteria

Classic LFS syndrome criteria[37]	A proband with: • A sarcoma diagnosed before age 45 years and • A first-degree relative with any cancer before age 45 years and • A first- or second-degree relative with any cancer before age 45 years or a sarcoma at any age
Chompret Criteria[26, 38, 39, 40]	A proband with one of 4 scenarios: 1) A tumour belonging to the LFS tumour spectrum (soft tissue sarcoma, osteosarcoma, pre-menopausal breast cancer, brain tumour, adrenocortical carcinoma, leukemia or broncho-alveolar lung cancer) before age 46 years and ≥ 1 first- or second-degree relative with an LFS tumour (except breast cancer if the proband has breast cancer) before age 56 years or with multiple tumours or 2) Multiple tumours (except multiple breast tumours), two of which belong to the LFS tumour spectrum and the first of which occurred before 46 years or 3) Diagnosed with adrenocortical carcinoma, choroid plexus tumour or embryonal rhabdomyosarcoma of anaplastic subtype, irrespective of family history or 4) Diagnosed with breast cancer before 31 years

How is a CPS diagnosed?

In most cases, molecular testing will confirm the diagnosis. Targeted gene analysis versus whole genome approaches will depend on the specific clinical scenario. Occasionally, a combination of clinical features will suffice to make the diagnosis, even without genetic confirmation. However, identifying the exact genetic alteration can be useful to establish a genotype-phenotype correlation. In other words, certain genetic mutations are known to predict the occurrence or severity of specific cancer types within a given syndrome. Such genotype-phenotype correlations are known for many, but not all, CPSs. For example in VHL, truncating and missense mutations confer a higher risk of renal cell carcinoma (RCC), whereas deletions in the gene are associated with a decreased risk of RCCs. Prenatal diagnosis can also be performed in situations in which the genetic alteration is known.

What are the benefits and risks related to the diagnosis of a CPS?

Many studies have described the risks related to the diagnosis of a CPS, including physical and psychosocial factors. During the diagnostic phase, genetic testing results are not always straightforward as they can often be of uncertain meaning (variants of uncertain significance (VUS) or noninformative).[29,30] Whole exome or cancer gene panel sequencing, increasingly used methods for molecular testing, may lead to the discovery of other genetic mutations in the patient which are not related to the actual condition but have a significant impact on the person's health. When a person is identified with a CPS, they are forever "labeled" as such. Social boundaries, including employment and insurance discrimination, are critical concerns for this population, notwithstanding the introduction of genetic non-discrimination legislation in many countries (currently under review in Canada's House of Commons).[41] In children, appropriate timing of genetic testing should be carefully evaluated according to the age at which cancers arise in a given syndrome and the possibility of using surveillance measures.[30,42] On a psychological and emotional level, living under the shadow of a "Damocles' sword" is extremely challenging. The constant and lifelong threat of a cancer diagnosis in a person or their loved ones can have a profound impact on their daily life and choices. Physicians need to be aware of these factors and address them in a serious manner. Allied health professionals, such as psychologists and social workers, are an essential part of the multidisciplinary management of this population.

Although, knowledge of a CPS may lead to significant anxiety and major life changes, knowledge is also power. Identifying a CPS is the key to proper medical management, surveillance, counselling, and education, which are all important factors affecting the overall outcome.

What can I do to prevent a cancer from arising in a patient with an inherited cancer syndrome?

Due to the inherent cancer risk conferred by the patient's mutated gene(s), the prevention of tumours is a complex measure that is most often impossible. In certain CPSs, risk-reducing surgery is an option because of the extremely high risk of developing a specific cancer type. For example, in familial adenomatous polyposis, a colectomy may be a suitable option to prevent a colorectal cancer. Likewise, bilateral mastectomy may be an option for a patient with a germline mutation in a BRCA gene. The balance between the risks and benefits needs to be carefully assessed in each clinical scenario. Minimizing potential toxic exposures, such as excessive sunlight, tobacco, or unnecessary radiation, is another important preventative measure.[43]

If I cannot prevent a cancer from occurring, how can I help my patients?

Cancer surveillance and education are the two key elements in the management of patients with CPSs. Specific tumour surveillance protocols have been created for various CPSs. These are designed for early detection of the malignancies known to be associated with a given inherited cancer syndrome, with the ultimate goal of reducing mortality and treatment-related morbidity.[44] The age at tumour presentation and the cancer prevalence are usually taken into account in the development of these guidelines. The surveil-

Table 3. Li-Fraumeni syndrome tumour surveillance protocol ("Toronto protocol"), adapted from Villani et al, 2016[44]

CHILDREN (0-18 YEARS)		
Adrenocortical carcinoma	Ultrasound abdomen and pelvis Blood tests: 17-OH-progesterone, total testosterone, dehydroepiandrosterone sulfate, androstenedione 24 hour urine cortisol level, if feasible	q 3-4 months
Brain tumour	Brain magnetic resonance imaging (MRI)	q 1 year
Soft tissue and bone sarcoma	Rapid whole body MRI	q 1 year
Leukemia/lymphoma	Blood tests: complete blood count, sedimentation rate, lactate dehydrogenase	q 3-4 months
General assessment	Complete physical examination with anthropometric measurements plotted on a growth curve, signs of virilisation and full neurological assessment	q 3-4 months
Prompt assessment with primary care physician for any medical concerns		
ADULTS (18 YEARS +)		
Adrenocortical carcinoma	Ultrasound abdomen and pelvis Blood tests: 17-OH-progesterone, total testosterone, dehydroepiandrosterone sulfate, androstenedione 24 hour urine cortisol level, if feasible	q 3-4 months (18-40 years)
Brain tumour	Brain MRI	q 1 year (18 years +)
Soft tissue and bone sarcoma	Rapid whole body MRI	q 1 year (18 years +)
	Ultrasound abdomen and pelvis	q 3-4 months
Colorectal cancer	Colonoscopy	q 2 years (25 years or 10 years before the earliest known colon cancer in family, whichever comes first)
Breast Cancer	Self breast examination	q 1 month
	Clinical breast examination	Bi-annually (20–25 years, or 5–10 years before earliest known breast cancer in family, whichever comes first)
	Mammography[1] and breast MRI screening[2]	q 1 year (20–75 years, or 5–10 years before earliest known breast cancer in family, whichever comes first)
Melanoma	Dermatologic examination	q 1 year
Leukemia/Lymphoma	Blood tests: complete blood count, sedimentation rate, lactate dehydrogenase	q 3-4 months
General assessment	Complete physical examination	q 3-4 months
Prompt assessment with primary care physician for any medical concerns		

[1]Breast ultrasound with mammography as indicated by breast density, but not instead of breast MRI or mammography.
[2]Breast MRI to alternate with annual rapid whole-body MRI (one scan every 6 months).
#Consider risk-reducing bilateral mastectomy

lance modalities used are also carefully chosen and should comply with certain criteria including accessibility, minimal radiation exposure and risk for the patient, adequate test sensitivity/specificity, and cost-benefit. These features are applicable to any screening procedure in the population. The tumour surveillance protocol for LFS is outlined in Table 3. This surveillance protocol, developed in Toronto in the early 2000's, was recently demonstrated, after an observation period of 11 years, to significantly increase long-term survival and decrease morbidity in patients with LFS. The protocol has been adopted in multiple centres around the world with similar beneficial results.

Published tumour surveillance guidelines exist for many CPSs including familial adenomatous polyposis, overgrowth syndromes, Lynch syndrome, hereditary pheochromocytoma/paraganglioma syndrome, tuberous sclerosis, and VHL. Because this is a rapidly evolving field and because each CPS is a rare entity in itself, most of the surveillance protocols are based on literature review and expert opinion. Proper validation studies have been undertaken for various protocols, but this is a work in progress.

Family and patient education cannot be underestimated in the management of CPSs. Educating and offering support to these families is the key to empowerment. The inheritance

pattern, the cancer risks, the tumour surveillance procedures, and the optimal lifestyle changes are important discussion points to have with the family. A genetic counsellor is again essential for the education of these families. Furthermore, ensuring that these patients undergo regular medical visits and are prompted to seek medical services in the case of a change in their health status is important and may even diminish the disease-related anxiety.

Finally, ongoing research aimed at better describing and gaining insight into the molecular defects related to tumorigenesis is essential. Animal models have been instrumental in understanding the links between a genetic defect and cancer phenotypes. They are also extremely helpful for the evaluation of toxic effects and efficacy of possible novel therapeutic agents.

When a cancer arises in a patient with a CPS, how do I manage it?

In most cases, tumours are managed in the same way as their sporadic counterparts. Certain inherited syndromes, especially those in which there is a defect in DNA repair, warrant the limitation of therapeutic modalities such as radiation. Unfortunately, many chemotherapeutic agents are associated with severe toxicity and increased tumour risk in this context, making treatment decisions for these patients particularly challenging. Staging, evaluation of tumour response, and surveillance during and after the diagnosis of a cancer requires the use of imaging techniques, some associated with radiation exposure. These should be used judiciously in order to minimize further tissue damage and risk of secondary malignancies. This concept is essential in LFS, where radiation is believed, though not as yet definitely proven, to increase the risk of new tumour development.

In certain circumstances, having a CPS opens the door to targeted therapy, thereby broadening the therapeutic arsenal. Targeted agents include medications that act on specific components of the altered molecular pathways related to tumorigenesis. For example, Sunitinib, a tyrosine kinase inhibitor known to inhibit the action of growth factor receptors, is used for patients with VHL diagnosed with clear cell renal carcinoma.[45] At this point in time there are no targeted agents used in patients with LFS as drugs do not readily target p53 itself, although much research is still ongoing. Likewise, there is active and exciting research evaluating the implicated molecular pathways and possible therapeutic agents for many other inherited cancer syndromes.

After going through the who, what, why, and how of the CPSs and LFS, you are now ready to evaluate and discuss the management and surveillance options for your patients. Realizing the importance of research in this growing and exciting field, you have also found the answer to how to spend your upcoming summer months: a research elective in cancer genetics!

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