Book Review: A Family's Cancer Ordeal, and a Genetic Enigma

In "A Fatal Inheritance" Lawrence Ingrassia chronicles his family's legacy of cancer, and the quest to find the culprit.

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When the Godwin sisters would visit their grandmother Jeanne in Carson City, Nevada, when they were growing up in the 1970s, Jeanne would pull out the dreaded juicer. She'd pulverize a mixture of carrot, celery, and spinach juice for the girls, then coax them to drink it. The sisters hated the concoction, but choked it down anyway, because they didn't want to upset their grandmother: Jeanne had lost her husband and two of her three daughters to cancer, and she hoped that this healthy mixture would save her granddaughters from the rest of her family's fate.

Jeanne didn't know it at the time, but diet hadn't caused her husband's and children's deaths. Her family were the unlucky carriers of a mutation on the p53 gene. When it's working, p53 acts as a tumor suppressor, stamping out malignancies before they can grow and spread. This gene is so important that one scientist called it the "guardian of the genome." People with the mutation, which causes an extremely rare disorder called Li-Fraumeni Syndrome, have a defective p53 gene, which means no brakes on tumors flourishing in their bodies. Families with this syndrome often lose a cascade of loved ones to breast cancer, lung cancer, pancreatic cancer, and more.

Lawrence IngrassiaCourtesy of Vicki Ingrassia

Lawrence Ingrassia hails from one of these families. He was spared the p53 mutation, but he lost his mother, two sisters, his brother, and a nephew to various cancers. Ingrassia, a Pulitzer Prize-winning journalist formerly with The New York Times and The Wall Street Journal, decided to chronicle his family story as well as explore the discovery of Li-Fraumeni Syndrome and cancer research in general. The result is "A Fatal Inheritance: How A Family Misfortune Revealed a Deadly Medical Mystery," a braided narrative in which Ingrassia charts the loss of his family as well as the tale of the scientists who turned cancer from an obscure yet burgeoning public health issue into one of the most-studied diseases of our time.

At its heart, the book creates a tense frisson as it chronicles a series of massive scientific breakthroughs, none of which successfully saved Ingrassia's family or the other families in this narrative. Ingrassia describes it aptly when he writes, "The story of Li-Fraumeni Syndrome and, more broadly, of cancer research isn't one story, but two. It is both a heartbreaking story of family loss and an inspiring story of human achievement."

Courtesy of Henry Holt and Company

A hundred years ago, the landscape for cancer research looked very different. Although almost everyone now has heard of BRCA and other genetic causes of cancer, researchers often dismissed the idea that cancer might be hereditary in those early days. As Nobel laureate Peyton Rous proclaimed in 1966, viruses and environmental factors might cause cancer, but not genetics: "Numerous facts, when taken together, decisively exclude this supposition," he said.

But two researchers at the National Cancer Institute, Frederick Pei Li and Joseph Fraumeni Jr., thought otherwise. In 1967, Li and Fraumeni heard about a father and baby who were both receiving treatment for cancer nearby in Baltimore. It turned out this pair hailed from the Kilius family, a sprawling clan scattered across the United States (which includes Jeanne, the grandmother who tried to stave off cancer by making her granddaughters drink a vegetable brew).

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Li and Fraumeni started tracking down each of the Kilius branches to find cancer occurrences. What they found was stark: Over five generations, 14 out of 35 members of this family had developed various cancers and 10 had died in their 40s or earlier. Although some of their colleagues wrote it off as a fluke and others scorned them for chasing genetic causes of cancer, Fraumeni and Li began the search for more families with abnormally high cancer instances while also trying to discern what was behind these clusters. They scoured America for suspected Li-Fraumeni families, then gathered blood and tissue samples to test for mutations.

Meanwhile, other researchers were cracking the mysteries of p53, discovering that it was not an oncogene, or cancer-causing gene, but rather a cancer-suppressing gene. After learning about p53, the Li-Fraumeni team homed in on it, painstakingly scrutinizing their samples to sequence the gene and find the mutation, no matter that this was "repetitive and monotonous work."

Finally, in 1990, Li and Fraumeni got their vindication. Science published a paper about the mutation, and headlines followed that trumpeted their discovery that, without doubt, a genetic defect played a role in certain cancers.

In the midst of this tale of scientific rivalry and discovery, Ingrassia deftly weaves the story of his own family, as well as the Kiliuses. He records the idiosyncrasies and joie de vivre that made his relatives so vividly human: his brother Paul's zeal for cars, his sister Angela's bond with her best friend from college, his other sister Gina's "magic brownies," which she brought to other chemo patients for nausea management.

He also spares no details of their illnesses and deaths. The image of Angela's family lowering her "naked and swollen body into the tub" in the last weeks of her life will be painfully legible to anyone who's witnessed a loved one wasting away from cancer. In fact, one weakness of the book is that Ingrassia's chapters about his own family are so finely observed and vulnerable that they sometimes overshadow the stories of the Kilius clan and the scientific discoveries.

In the second part of the book, Ingrassia charts his narrative of cancer research up to the present day, exploring, for example, how the discovery of Li-Fraumeni Syndrome paved the way for scientists to find better-known genetic mutations like BRCA. But he also chronicles an uncomfortable truth about cancer research: Even now, in 2024, the best that the medical establishment can offer BRCA patients is preventative mastectomies.

And therein lies the tragedy of Ingrassia's narrative. Since the 1990s, cancer researchers have tried to find a cure or treatment to help Li-Fraumeni families. And they are making progress: conducting research on gene therapies, like injecting a normal version of the p53 gene into a tumor to kill cancer cells; the development of the successful Toronto Protocol, which recommends that families with the mutation undergo intense, regular monitoring to catch tumors early; and CRISPR, a technology that allows scientists to edit mutations out of genes, which researchers are studying as a potential treatment.

These measures have certainly helped families suffering from Li-Fraumeni and other disorders. A 2011 study found that the Toronto Protocol, for example, was found to be extremely effective in detecting and treating cancers early. Seven out of seven patients in the study who opted for the screening and developed cancer survived, while of the 10 patients who opted out of the screening and got cancer, only two survived. But these measures are not enough, according to families.

Ingrassia recounts a stirring, disturbing scene from 2010, when an LFS family member named Oliver Wyss spoke at a workshop to a roomful of researchers. Despite undergoing genetic testing and multiple rounds of treatment, Wyss' son had died of cancer at age 3 in 2008; his daughter would die five years later, age 11. Wyss admonished the researchers for not doing more, saying, "It is not acceptable to me. It's not acceptable to my wife. It's not acceptable to the other family members who are running out of patience. So it should not be acceptable to you.''

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cure or treatment to help Li-Fraumeni families. And they are making progress, but according to families, these measures are not enough.

Years later, writes Ingrassia, the scientists at that gathering remembered that speech like it was yesterday. Even now, Li-Fraumeni families are left with not much more than the same ethical conundrums that dogged their forebears: whether they should avoid having children, whether it's better to get tested for the mutation and screened regularly for cancer, or whether to live their lives.

Ingrassia's feelings are palpable. It's clear that he feels grief that advances in cancer treatments didn't come soon enough to save his family; guilt for not learning about Li-Fraumeni Syndrome sooner; melancholy over his siblings' deaths; and a responsibility to capture them on the page before he's gone, too.

And yet Ingrassia ultimately ends with cautious optimism that in the coming decades, those cures will come. He dreams of a future when "humanity may recall a primitive time when doctors couldn't treat people born with debilitating or life-threatening genetic disorders simply by injecting them with a drug to fix the mutation, just as we now look back to periods in history when surgeons operated on patients without anesthesia to ease the pain and without antiseptics to prevent deadly infections."

With some two million new cancer cases and 600,000 cancer deaths every year in the United States, we can certainly hope that Ingrassia is right.

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This article was originally published on Undark. Read the original article.

To read a Cancer Health interview with Ingrassia, see "Amid His Family's Fatal Cancers, an Author Finds Genetics, Grief and Hope."
