The genetic mutations associated with more than 50 hereditary cancer syndromes, which play a major role in the development of about 5% to 10% of all cancers, have been identified, and genetic tests can help tell whether a person from a family with such a syndrome has one of these mutations.
Angelina Jolie carries a mutation of the BRCA1 gene, which sharply increases the risk of breast and ovarian cancer.

Angelina Jolie made headlines in May when she underwent a preventive double mastectomy after learning that she carries a mutation of the BRCA1 gene, which increases the risk of breast and ovarian cancer.

The Hollywood actress brought public attention to a genetic and hereditary mutation for breast cancer, but less well-known is that more than 50 hereditary cancers have been identified.

While breast and ovarian cancers receive the lion’s share of publicity, they are not the leading causes of cancer death worldwide.

Digestive cancer, including gastric cancer, is second only to respiratory cancer in terms of estimated deaths. Almost 1 million people are diagnosed with a form of digestive cancer each year, and of these, about 700,000 will lose their lives. Digestive cancer is the fourth-most common cause of cancer worldwide, and gastric cancer has been identified as one of the known 50 hereditary cancers associated with gene mutation.

**DIGESTING STOMACH CANCER**

Karen Chelcun Schreiber, founder of the nonprofit organization No Stomach for Cancer, aims to shine a spotlight on gastric cancer. One of her goals is for people to know as much about stomach cancer risk and prevention as they do about breast cancer risk and prevention.

“The organization’s goals are to raise money to advance stomach cancer research, raise awareness about stomach cancer, and advance education about stomach cancer, not only in the general public but also in the medical community,” she says. “We provide information, resources, and support for patients and families affected by stomach cancer, and continue to build a support network — a worldwide community — where they can support one another and become involved in raising awareness about this disease.”

No Stomach For Cancer has been extremely active since its inception in 2009, and in November 2010 it successfully championed and celebrated the first official Stomach Cancer Awareness Month in the United States. There is a great deal of focus on food, nourishment, and family during the holidays, and that can be challenging for people dealing with stomach cancer, and for those living without a stomach.

Supporters hope that greater awareness and knowledge will lead to earlier detection of stomach cancer, which is directly associated with higher long-term survival rates, and that the money raised for stomach cancer research will result in better detection, treatments, improved survival rates, and ultimately a cure for this deadly disease.

Ms. Chelcun Schreiber’s crusade began in September 2007 after her brother, Greg, at 56, became the second person in the family to be diagnosed with stomach cancer. Their mother had died in 1982 from the disease at the age of 52.

“The doctors had told us that stomach cancer was rare, so I was curious as to why two people in our family had gotten this cancer,” she says. “I didn’t know anything about stomach cancer. I was looking for more information, and I came upon an article from Stanford University about this hereditary cancer syndrome caused by a gene mutation. I strongly suggested that my brother be tested, and he was positive. After that a lot of family members started getting tested and most of us had positive results.”

Ms. Chelcun Schreiber herself was positive for the CDH1 gene mutation, which put her at a more than 85% risk of developing a form of stomach cancer called hereditary diffuse gastric cancer (HDGC). The only current treatment for those with this cancer syndrome is preventive removal of the stomach.

Genetic Testing for Hereditary Cancer Syndromes

- Genetic mutations play a role in the development of all cancers. Most of these mutations occur during a person’s lifetime, but some mutations, including those that are associated with hereditary cancer syndromes, can be inherited from a person’s parents.
- Inherited mutations play a major role in the development of about 5% to 10% of all cancers.
- The genetic mutations associated with more than 50 hereditary cancer syndromes have been identified, and genetic tests can help tell whether a person from a family with such a syndrome has one of these mutations.
- A genetic counselor, doctor, or other healthcare professional trained in genetics can help an individual or family understand genetic test results.

Source: National Cancer Institute
particular gene mutation.

150 families worldwide reported to have this mutation that three out of every four CDH1 gene mutated 1% to 3% of cases of gastric cancer are caused by HDGC. The CDH1 mutation is a dominant gene, meaning that children of those with the mutation have a 50% chance of inheriting the mutation as well. It is estimated that three out of every four CDH1 gene mutation carriers will go on to develop gastric cancer, with an average age at diagnosis of 38.

Ms. Ford del Rio’s family is one of only 150 families worldwide reported to have this particular gene mutation.

She and seven other family members have tested positive for the hereditary gene, which traces back, as far as they know, to her paternal grandfather. Some of the family members who have tested positive have or are planning to undergo prophylactic gastrectomy.

“My gastroenterologist never heard of it, my gynecologist never heard of it, and my other doctors never heard of it,” Ms. Ford del Rio says.

Ms. Ford del Rio credits the No Stomach for Cancer organization with providing her and her family with a tremendous amount of support.

(RESEARCH IN GASTRIC CANCER)

About 15% of stomach cancers occur in patients with a family history of stomach cancer. Several genes have been implicated in gastric cancer. One of these is the HER2 gene, which is typically associated with breast and ovarian cancer. Roche and Genentech’s Herceptin (trastuzumab) was approved in October 2010 to treat HER2-positive gastric cancer.

The development of other therapies for gastric cancer have experienced some recent setbacks because of less than positive clinical results. The most recent setback was Glaxo-SmithKline’s announcement in June of this year that Tykerb in combination with chemotherapy in patients with HER2-positive advanced gastric cancer did not meet the primary endpoint of improved overall survival compared with chemotherapy alone.

“This is an extremely difficult-to-treat oncology indication,” says Rachel Webster, D.Phil., senior director, oncology group, at Decision Resources. “This is not dissimilar to what we see in some other indications with short survival times and in tumor types that are chemo resistant. Part of the problem with gastric cancer is that the majority of patients are not diagnosed until an advanced stage. But when symptoms are more overt, advanced or metastatic disease has likely developed.”

A December 2012 Decision Resources report predicts that the gastric cancer therapy market will experience slow annual growth from 2011 to 2016 (2.4%) but then rapidly expand thereafter, achieving annual growth of 13.7% from 2016 to 2021.

Dr. Webster points out that those therapies that have failed to meet endpoints in gastric cancer have had demonstrated success in other oncology indications, such as breast, colorectal, and renal cancers.

Research into next-generation HER2 therapies continue. For example, Genentech’s Pertjeta (pertuzumab) was approved in June 2012 to treat HER2-positive metastatic breast cancer in combination with Herceptin.

NO STOMACH FOR CANCER

Since its inception in 2009, No Stomach For Cancer (NSFC) has been an advocate and voice for those affected by gastric cancer.

Each November, NSFC encourages patients, caregivers, families, friends, businesses, and organizations to participate in Stomach Cancer Awareness Month in a variety of ways: putting a face to the disease by sharing personal stories through local, national, and international media; through awareness activities in their neighborhoods and local communities; through active engagement on its Facebook pages and Website forum and other social media; through third-party events; and through participation in the annual No Stomach For Cancer Walk.

The second annual No Stomach For Cancer Walk will be Nov. 2, 2013, and will kick off the 4th Annual Stomach Cancer Awareness Month.

“It has been very exciting to watch the momentum of this important awareness initiative building,” says Karen Chelcun Schreiber, founder of the organization. “We see growing interest and involvement by people who care about this cause, not only in the United States but also in countries throughout the world. The word is getting out and the passion to help others and to make a difference is evident everywhere.”

For more information or to learn how to join the walk, please visit nostomachforcancer.org.
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Trastuzumab has paved the way for other HER2-targeted therapies in gastric cancer, Ms. Webster says. “We expect the HER2-positive segment to become very crowded and competitive and to be dominated by Roche,” she says. “We envision that the HER2-positive segment is going to mirror what is happening in the HER2-positive breast cancer space.”

There are other promising therapies in the pipeline addressing the larger segment of HER2 negative gastric cancer.

One such product is Lilly’s ramucirumab, which in its first Phase III trial demonstrated overall survival and also showed prolonged progression-free survival. This monoclonal antibody is being studied as a second-line treatment in patients with metastatic gastric and gastroesophageal junction cancers.

Decision Resources expects this product will secure robust uptake in the HER2 negative market, with more than $250 million in sales, or about 10% of the market, in 2021.

Developing treatments for gastric cancer has historically been a challenge due to a limited understanding of the underlying molecular mechanisms driving the disease, says Chris Bowden, M.D., VP, bio-oncology, clinical development, at Genentech.

“But as we learn more about the molecular basis of gastric cancer, the treatment landscape is beginning to change,” he says. “For example, now people diagnosed with gastric cancer can have their tumor tested to confirm HER2 status and determine if they could be a candidate for Herceptin.”

Another promising area of research is addressing c-Met, which makes a protein that some tumors use to grow and spread. Two therapies under study are Genentech’s onartuzumab and Amgen’s rilotumumab, which Decision Resources researchers expect to launch for c-Met-overexpressing gastric cancer in 2017.

Genentech’s onartuzumab is a first-in-class monoclonal monovalent antibody in Phase II and Phase III trials. It is designed to inhibit Met signaling in cancer cells by binding to the extracellular domain of Met, thereby blocking HGF-mediated activation.

The Met receptor (also known as c-Met) is a protein on the surface of cells that is associated with cell growth, survival, motility, migration, and invasion. When overexpressed, Met may play an important role in the development of cancer.

“Onartuzumab is the first investigational antibody designed to specifically bind to the Met receptor and inhibit Met signaling,” Dr. Bowden says.

Onartuzumab is a unique one-armed anti-
Eight members of the extended Napolitano family carry the gene mutation. Another 12 relatives have yet to be tested for the gene. Lauri Ford del Rio (right) and her cousin Deb Napolitano hope to be role models to all of them.

Deb Napolitano and Lauri (Napolitano) Ford del Rio

prophylactic gastrectomy, in other word, having their stomachs removed.

Unfortunately, CDH1 also is linked to lobular cancer, which can lead to breast cancer. Fortunately, Ms. Ford del Rio has an incredible support group and she and her cousin underwent the gastric surgery together, shared the intimacy of recovery, and were each others’ cheerleaders.

The two cousins will once again face the daunting experience of undergoing another radical surgery together. The two cousins are each having double mastectomies.

“We decided it doesn’t seem fair that if we went through all we did to remove our stomachs then get breast cancer,” Ms. Ford del Rio says.

And when Ms. Ford del Rio talks about her journey she does so without self pity or remorse. She is remarkably up-beat, positive, and eager to elevate the conversation around gastric cancer education.

The only time Ms. Ford del Rio reveals any crack in her good-humor is when she speaks about her three children. Because the gene is dominant, they have a 50% chance of being positive. She adds encouragingly that because her sister tested negative for the gene, it stops with her and Ms. Ford del Rio’s niece and nephew are not at risk.

“The interesting thing is that my dad’s only remaining brother who is 90 years old, who also tested positive is among the 13% who never manifest the disease, and it’s his three kids — my cousins — who also tested positive,” she says.

When people ask her why she would undergo such a radical surgery, her response is: “With an 87% chance that I was going to get this horrible horrible cancer and knowing that I was going to die if I did, to me it was a no-brainer.”

Removing a stomach is a major procedure, but a relatively low-risk one, says Dr. Sam Yoon, the surgeon who operated on Ms. Ford del Rio and her cousin Deb Napolitano, at Memorial Sloan Kettering Cancer Center in New York.

“It turns out the stomach is less crucial than you might think, because most nutrients are absorbed through the small intestine,” he says. “The stomach is basically a reservoir for the food eaten. Patients who have had their stomachs removed can eat three meals a day. Without a stomach they can lead a pretty normal life, but they need to eat a little bit constantly. I tell patients they’re going to need to graze like a cow.”

And how is life after surgery a year later? Ms. Ford del Rio says she is adjusting without a stomach by amending her eating habits, monitoring her vitamin B12 and calcium, and most importantly, living life to its fullest.

Source: Facing Our Risk of Cancer Empowered Inc. (FORCE). FORCE has a printable page for sharing information with relatives. For more information, visit acingourrisk.org.

SHARING FAMILY INFORMATION

Families share more than genes, physical features, and medical traits.

Other common elements — backgrounds, relationships, and dynamics — sometimes affect communication between family members.

In some families, cancer, breasts, and ovaries are considered very private matters never to be discussed. Cancer and other illnesses are often associated with a stigma in our society. Some family members may be superstitious about discussing cancer, believing that may invite the disease and make it more likely to happen. This lack of communication can impede sharing of critically important health information between relatives. Despite these challenges, it is important to share medical information with relatives. Cancer and many other diseases can have a hereditary component. Screening or risk-management recommendations are different for people who are considered “high risk” due to a family history.

The best way to discuss health information is individual and depends on your relationship with relatives. Here are some tips for sharing:

• Be sensitive to family members’ situations and feelings.
• Give relatives the names of genetics specialists in their area to ensure that they receive up-to-date information.
• Avoid pressuring relatives to make a particular decision.
• Respect their right to gather information from experts and make their own informed decisions.
• Prepare for your conversation ahead of time by writing down what you want to tell them.

Source: Facing Our Risk of Cancer Empowered Inc. (FORCE). FORCE has a printable page for sharing information with relatives. For more information, visit acingourrisk.org.
body targeted against the c-Met receptor. Antibodies usually have two arms, each of which can bind to a target.

“But preclinical studies of Met revealed that two-armed antibodies caused Met receptors to form pairs (dimerize) and activated Met signaling, which led to uncontrolled cell replication and spread,” Dr. Bowden says. “To address this problem, Genentech researchers created a one-armed antibody that is designed to prevent Met signaling by blocking hepatocyte growth factor/scatter factor (HGF/SF) from binding to Met without causing Met receptors to form pairs.”

The company is investigating onartuzumab across a number of cancers. For gastric cancer, Genentech has initiated Phase II and Phase III trials that will compare onartuzumab plus mFOLFOX6 chemotherapy to mFOLFOX6 chemotherapy alone in people with previously untreated HER2-negative, Met-positive metastatic gastric cancer.

Another company researching Met expression is Amgen. Last year, the company announced results from an exploratory biomarker analysis evaluating Met expression as a predictor of clinical response to rituxumab, a human monoclonal antibody. This analysis, conducted on a previously reported Phase II study of rituxumab in patients with locally advanced or metastatic gastric or gastroesophageal cancer, showed that treatment with rituxumab in combination with chemotherapy improved median overall survival in patients whose tumors exhibited high Met protein expression.

Amgen plans to conduct a Phase III study to confirm the efficacy of rituxumab in advanced gastric and gastroesophageal cancer with high Met expression. The company has teamed with Dako to develop and evaluate the use of a companion diagnostic test.

Decision Resources analysts anticipate that Roche’s onartuzumab and Amgen’s rituxumab will capture a significant patient share within one of the largest and currently underserved drug-treatable gastric cancer populations — the first-line metastatic HER2-negative population (about 83% of first-line patients). Their uptake will be the primary driver of market growth over the second half of Decision Resources’ forecast period. Combined, these agents will hold one-third of the market in 2021. Furthermore, these agents will be prescribed in combination with standard chemotherapy regimens and will, therefore, contribute additional sales rather than erode the sales of currently marketed therapies.

In the area of the gastric cancer caused by CDH1 gene mutation, research is just beginning. The CDH1 gene, located on chromosome 16, normally encodes for a protein called E-cadherin. The normal function of E-cadherin is to allow cells and tissues to adhere to one another.

“CDH1 is mutated in diffuse gastric cancer and lobular breast cancer, and down regulated in many other late-stage epithelial cancers,” says Parry Guilford, director of the Centre for Translational Cancer Research, Cancer Genetics Laboratory, at University of Otago in New Zealand. “Although the loss of E-cadherin increases tumor development, we believe it also causes vulnerabilities in the cancer cell. These vulnerabilities appear to be largely associated with weaknesses in the function of the cytoskeleton.”

Dr. Guilford says five classes of drugs look promising for this syndrome — HDAC inhibitors, JAK inhibitors, EGFR family inhibitors, PI3K inhibitors, and Ros1 inhibitors — and researchers are beginning work to validate those drugs with in vitro assays.

“We believe these drugs/drug targets will be important for the chemoprevention of HDGC, but also the treatment of all diffuse gastric cancers and lobular breast cancers,” he says. “The HDAC inhibitors are most promising. We have strong data for several drugs from this class including entinostat, mocetinostat, vorinostat, and pracinostat. As well as the HDAC inhibitors alone, we have observed that vorinostat in combination with the microtubule stabilizing agent Taxol has a powerful effect on CDH1 negative cells compared to wild type cells.”

No Stomach for Cancer, with matching funding from the De Gregario Family Trust, is supporting a 114,000-compound screen against the isogenic MCF10a cells. Researchers hope to find drug candidates that work on any tumor with CDH1 mutation. This research is being done by Dr. Guilford and his colleagues. No Stomach For Cancer has provided a grant of $20,000 for this research.
Cubixx®: An Innovative Solution for Specialty Pharmaceutical Inventories

By Christopher Flori

No doubt about it. This is an exciting time for specialty pharmaceuticals. Many new products are nearing the end of the pipeline. Some of these new medications will offer improved benefits that enhance the quality of patients’ lives. Those benefits are easy to see. But other innovations have already been introduced, providing benefits specialty pharmacies and healthcare providers may not easily see. The Cubixx consignment system from ASD Healthcare is one of those innovations.

Cubixx is a storage and monitoring system designed to help hospitals and specialty pharmacies manage and track inventories of high-cost, complex biological drugs. Cubixx provides custom-made refrigerators to store the specialty inventory. Inside, each box of product is tagged with a radio-frequency identification tag (RFID), which contains product data. With an RFID tag, no one needs to scan each box; it is scanned automatically as it’s removed from inventory. The Cubixx system tracks brand, IU, lot number, expiration date and individual serial numbers. This lets manufacturers, distributors and sellers follow each product from the manufacturing plant to the patient who uses the medication.

Cubixx works on a consignment model. In other words, facilities or pharmacies pay for only what they sell. ASD Healthcare provides product to healthcare facilities such as hospitals, specialty pharmacies, HTCs, etc., and bills them only for the product actually used. The Cubixx system reduces the need for facilities to purchase and hold these expensive inventories, which may or may not be sold. Cubixx also helps eliminate the added expense of lost, stolen or expired products.

The distribution of specialty pharmacy product presents many unique logistical challenges with many medications requiring “cold-chain” handling to keep them refrigerated in transit. These medications are also very expensive. Stakeholders—from physicians to payers and manufacturers—want clear visibility to see how these products are used. Cubixx can track this information on each specialty product as it is sold from the manufacturer to the distributor to a health care facility and finally to a patient.

ASD Healthcare has a 20-year history of serving the specialty pharmaceutical sector. We’re committed to finding innovative solutions for the facilities that care for patients who require specialty therapies. The Cubixx consignment system is one of these innovations. By helping facilities reap so many benefits, Cubixx helps them provide the highest-quality care to the patients they serve.

The Cubixx system reduces three major challenges for facilities and pharmacies.

Economic

The benefits of Cubixx consignment inventory are significant. Paying for products only when they’re used, while still having access to the range of products needed, provides savings for healthcare facilities and specialty pharmacies alike. Freight expenses and financial losses due to expired or unsold products are eliminated. With Cubixx, rather than invest in product and holding expensive inventory, facilities can redirect their money for other uses.

Operational

Cubixx does the heavy lifting for product reorders. It produces purchase orders, manages day-to-day product inventory and allows the facility to log onto the Cubixx website to view its inventory of products anytime. This takes the administrative burden off the healthcare facility or pharmacy staff.

Clinical

As one of the largest specialty distributors in the United States, we have access to commercial product and 340B product in a breadth and depth that gives clinicians the widest possible selections of products at their fingertips. This Cubixx benefit gives facilities instant access to more product options to meet a wider range of their patients’ needs.

Christopher Flori is Vice President of Business Innovation at ASD Healthcare, an AmerisourceBergen Specialty Group. For more information on Cubixx, please contact him at 469.365.7841 or Chris.Flori@asdhealthcare.com.

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