Over 90 per cent of drugs don't work for half of patients, and adverse drug reactions cause more than 100,000 deaths in North America each year. When drugs are made to measure, treatments are safer and more effective.

drugs made to measure

When it comes to drugs aimed at treating serious diseases, such as cancer and heart disease, one size does not fit all. DNA technology now allows doctors to select medicines that work better for you and cause fewer side-effects. By Mark Witten

Imagine that – God forbid – you are diagnosed with a major ailment, such as breast cancer, heart disease or depression. Your doctor prescribes medication to treat it; you hope that this drug will help you recover fully. And you may – if you and your doctor are lucky.

The fact is that over 90 per cent of drugs don't work for half of patients. More alarmingly, many patients have adverse reactions to medications. These side-effects cause more than 100,000 deaths in North America each year. In other words, one size does not fit all when it comes to treating illnesses with drugs. "It's antiquated to think a single dose affects each person the same way. That's old school," says Dr. Muriel Brackstone, a breast cancer specialist at the London Health Sciences Centre (LHSC) in London, Ont.

So what's new school? The emerging practice of personalized medicine – using your genetic blueprint to tailor drugs and dosages specifically to you.

Consider Enza Guevara. Last winter Enza learned she had breast cancer after her routine mammogram and ultrasound picked up a suspicious mass in her right breast. Enza, who has three sisters and two daughters, was shocked by the diagnosis. "There's no breast cancer in our family. I never in a million years would have expected this," says the >

ILLUSTRATION, IAN NAYLOR

47-year-old, who works for the Catholic Children's Aid Society in Toronto.

After having a lumpectomy, Enza met with Dr. Phil Bedard, a breast cancer specialist at Princess Margaret Hospital in Toronto, to review her treatment options. The good news was they had caught the disease early. She had Stage 1 estrogen receptor–positive cancer and her lymph nodes were clear. The biopsy results, however, indicated that the tumour was not Grade 1 (the slowest growing and least likely to spread). It was Grade 2. "They would usually recommend chemo for someone with Grade 2," she says. "But the doctor told me there are a lot of women who go through chemo for no reason." Dr. Bedard explained to Enza and her husband that she was a good candidate for a new test called Oncotype DX, which can help determine the risk that the cancer will recur within 10 years, based on the tumour's genetic makeup. The test provides more information about the risk of recurrence than pathology results alone,

> "If it wasn't for this test, I would have had to do the chemo."
>
> – *Enza Guevara*

and can help a woman make a more informed decision about whether or not to have chemotherapy. If Enza's risk score turned out to be low, she wouldn't need or benefit from the regimen. If it was high, chemo treatment would substantially reduce the risk that her cancer would come back.

"At first I was a little hesitant," says Enza, who hadn't heard of the test before and wanted to be sure it was reliable. "Another part of me thought that it would be wonderful if I didn't have to deal with chemo." After learning more, she decided to go ahead.

A specimen of Enza's tumour was sent to Genomic Health in California and analyzed to determine the level of activity in 21 of her tumour's genes. Many of the genes are related to how quickly the cells divide. The test gives patients a recurrence score from zero to 100: Low-risk scores fall within one to 17; high-risk scores are 31 or higher. "My biggest worry was that the score would be high and I would know the prognosis wasn't good," she says. Within about two weeks, Enza got the results: a recurrence score of 15, which meant there was only a 10 per cent chance the cancer would return within 10 years (with tamoxifen treatment), and she wouldn't need chemotherapy. "My husband and I were both ecstatic. If it wasn't for this test, I would have had to do the chemo."

Personalized medicine dramatically improved Enza's treatment by matching the drug therapy she needed to the DNA signature of her tumour. New drugs targeted to the genetic characteristics of tumours – given only to patients who are likely to benefit – are saving lives and boosting the odds of recovery.

Two types of tests are making all the difference. Genotyping tests predict how well or how poorly a woman metabolizes a drug. These allow doctors to tailor her dose to get the most benefit and avoid harmful side-effects. Secondly, genetic-risk profiling can predict the odds that a woman will benefit from a specific therapy. These tests allow her to make an informed choice about the optimal medication and avoid unnecessary treatments.

The personalized medicine approach is now being applied to a number of medical issues, such as heart disease, blood transfusions, mental illness and many types of cancer. When drugs are prescribed to fit a woman's personal genetic profile, she can get timely access to better, safer treatments and avoid needlessly taking medications that are unlikely to work.

Breast cancer breakthroughs

There are various types of breast cancer – including those that are fuelled by female hormones and those that are not – and each has its own drug therapies and related suitability tests for those therapies. The drug Herceptin, first approved for widespread use in Canada in 2005, is a stellar example of a genetically targeted drug. It has transformed treatment and brightened the prognosis for women with HER2-positive breast cancer. This aggressive form of cancer affects about 20 per cent of all breast cancer patients. "Herceptin has been a miracle story. It has dramatically reduced the risk of recurrence for a group of patients who were difficult to treat," says Dr. Kathy Pritchard, a medical oncologist and breast cancer specialist at Sunnybrook Health Sciences Centre in Toronto.

Women with this type of breast cancer have tumours that make too much HER2 protein. These proteins act like antennas on the surface of cancer cells, making up a signalling pathway that makes the cells grow and multiply. Herceptin works by singling out these harmful proteins on breast cancer cells and blocking the growth signals. The drug also alerts the patient's immune system that it needs to destroy the targeted cells.

Unlike chemotherapy, which destroys all fast-growing cells, including healthy ones, Herceptin attacks only the bad cells that drive the cancer. It doesn't help women with other types of breast cancer.

Herceptin has saved many lives since provincial governments across Canada began covering the cost of the medication (for eligible patients), along with certain suitability tests, six years ago. **>**

Enza Guevara with her husband, Jorge

PHOTOGRAPHY: MONICA MCKENNA.
HAIR AND MAKEUP: KELLY MEREDITH FOR TRESEMMÉ HAIR CARE/JUDYINC.COM

By testing cancer cells (removed during a biopsy or surgery) for excess amounts of the HER2 protein, your doctor can determine if you'd benefit from the drug. Studies show it reduces the risk of breast cancer relapse by nearly half in women with early stages of the disease who receive chemotherapy. As well, the drug helps some women with metastatic cancer live longer.

Herceptin is a genuine breakthrough, but it's essential to know if it fits the tumour's genetic profile, because it's not without risks. Since it can cause serious heart problems in a small percentage of patients, your heart health should be monitored before and during treatment. These kinds of personalized treatments have also been developed for patients with certain types of colon cancer, lung cancer and leukemia, and they may be prescribed depending on the DNA of the tumour.

> "Now we can identify a woman who, in the past, would have been put on an ineffective treatment." – Dr. Muriel Brackstone

There are several options for women with other types of breast cancer and differing genetic profiles. Premenopausal women diagnosed with estrogen receptor–positive breast cancer are often prescribed tamoxifen, a drug used to prevent recurrence. Tamoxifen exerts its cancer-fighting effect when an enzyme in the liver converts the drug into its active form, endoxifen. Research shows that nearly 10 per cent of Canadian women don't make enough of the enzyme because of their genetic make-ups; therefore they're less able to convert the drug to endoxifen. If these women unknowingly take the standard dose of tamoxifen for five years, they probably won't benefit from the treatment and their cancers will be more likely to come back.

Dr. Richard Kim, a physician and specialist in clinical pharmacology at the LHSC, runs a personalized medicine clinic for breast cancer patients who are on tamoxifen therapy. There, Dr. Kim identifies women for whom tamoxifen would be effective, and does genotyping tests to learn whether a woman is a poor, low, normal or rapid metabolizer of the drug. He also measures her tamoxifen and endoxifen blood levels. "Now we can identify ahead of time a woman who, in the past, would have been put on an ineffective treatment, and look at other options," says Dr. Brackstone. "If the test shows a woman is a normal metabolizer, it gives reassurance that she'll really benefit from the therapy."

What are the options for women who metabolize the drug poorly? Doctors may recommend switching to another type of hormonal therapy, known as an aromatase inhibitor, to prevent recurrence. If a woman is premenopausal, she'll need to have her ovaries removed for aromatase inhibitors to be effective. "Another option is to increase the tamoxifen dose and see if the endoxifen levels reach the therapeutic range," says Dr. Brian Dingle, a breast and lung cancer specialist who sometimes refers patients to Dr. Kim's research clinic.

When chemotherapy is recommended, some women with breast cancer are undertreated, while others are overtreated. Unfortunately, cancer doctors often can't tell from pathology results alone whether certain patients (namely, women with early-stage estrogen receptor–positive breast cancer that hasn't spread to the lymph nodes) should or shouldn't have chemotherapy. "We know the averages, but that doesn't help us tailor treatment to the individual," says Dr. Bedard.

Dr. Bedard and other oncologists are using a new genomic test, called Oncotype DX (the same test Enza took), to help women make the best possible decisions when faced with an agonizing choice: undergo chemotherapy after having tumours surgically removed and deal with its hair loss, nausea, immunosuppression, and possible leukemia, infertility and premature menopause, or opt to go without it and risk a recurrence within the next decade. >

With the Oncotype DX test, women like Enza learn whether they have low-risk scores and would receive little or no benefit from chemotherapy, or high-risk scores and would be much more likely to benefit. Dr. Brackstone estimates that oncologists would change their treatment recommendations for eligible patients in about 30 per cent of cases if they were to start using this test. Many women who would otherwise be candidates for chemo wouldn't have to receive it. But other women, whose pathology results might suggest that chemotherapy isn't necessary, would be treated with it if their tumours' genetic signatures showed they were at high risk. About 10,000 breast cancer patients in Canada would be good candidates for the test each year and over 1,000 Canadian women have had it so far.

Ontario is the only province that currently pays for the test for eligible patients (it costs about $4,000). In other provinces, patients may get the test with help from private insurance reimbursement, but others may have to pay for it themselves.

Honing heart therapies

More than two million people in North America are prescribed the blood-thinning drug warfarin each year for ailments such as irregular heartbeats, heart valve replacements and blood clots that can lead to strokes or heart attacks. It's a life-saving drug, but it's dangerous too, because it has a narrow margin of safety. (Too much of the blood thinner can cause uncontrolled bleeding, while too little can result in a blood clot. Either one can kill.) "Warfarin is the most common cause of emergency hospital visits related to drug problems," says Dr. Kim, who uses gene-guided dosing to make treatment safer for patients referred to his personalized warfarin clinic at the LHSC.

Yet getting the dose right is tricky. The optimal dose for one woman can be up to 10 times higher than for another, due to individual variations in both a blood-clotting gene and a drug-metabolizing gene.

Dr. Kim analyzes the DNA of each of his patients, checking for variations in the two genes. He uses that information to help get the starting dose of warfarin right. About 30 per cent of his patients require a dose that is much higher or lower than the standard dose of five milligrams.

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Not coincidentally, patients who undergo personalized medicine tests to determine their starting warfarin doses have about a 30 per cent lower risk of being hospitalized than those whose doses are set by trial and error, according to a 2010 study published in the *Journal of the American College of Cardiology*. "We think we prevent at least a few strokes a year," says Dr. Kim, noting that the financial cost of a stroke to the individual and the medical system is about $50,000 in the first six months.

Another type of medication that Dr. Kim works with is called statins. These include the drugs Lipitor and Crestor, which are prescribed to more than three million Canadians to lower their cholesterol levels and reduce their risks of heart disease. But about 300,000 of those patients who take statins suffer from troublesome side-effects such as muscle aches or weakness. Some may even risk a life-threatening muscle injury known as statin-induced myopathy.

Heart patients who experience these debilitating side-effects can be referred to Dr. Kim's statin clinic, where he uses personalized medicine techniques to tailor treatments to them. He tests patients' DNA for variations in genes associated with these symptoms, and measures their statin levels as well. "We may switch the patient to another type of statin, or change the dose to avoid these side-effects and reduce the risk of severe muscle injury," he says. >

Personalized blood transfusions

People with conditions such as sickle-cell anemia, hemophilia, thalassemia and leukemia may need regular blood transfusions. But over time, their immune systems may develop resistance to the blood of many donors, because an imperfect blood match often causes an immune response. In the long run, this makes it difficult to find a close enough match, and can lead to immune reactions ranging from mild chills and fevers to life-threatening anaphylactic shock.

Héma-Québec, the province's blood services agency, has created the world's first blood bank that uses more accurate and precise genotyping to quickly find compatible matches for patients who require regular blood transfusions.

With the help of the Beaulieu-Saucier Pharmacogenomics Centre at the Montreal Heart Institute, Héma-Québec built a database of 28,000 frequent blood donors that includes the genotype for each donor's blood. This innovative matching tool takes the more than 5,000 otherwise difficult transfusions that need to be done each year and makes them much easier and safer. "Instead of having to test 100 blood samples to find the exact match, we now test three or four. It's saving time, money and lives," says Maryse St-Louis, a research scientist at Héma-Québec who helped develop the system.

Depression, drugs and DNA

When a doctor prescribes a drug to treat a mental illness such as depression or schizophrenia, some people will improve remarkably, others will not be helped and a third group may experience side-effects so bad that they stop taking their medications. Unfortunately, doctors generally can't predict who will be helped or possibly even harmed by a particular drug. So they must rely on trial-and-error prescribing to select the best medicine and the starting dose for each patient.

Dr. Daniel Mueller, a psychiatrist at the Centre for Addiction and Mental Health in Toronto, is pioneering a more precise approach to prescribing antidepressant and antipsychotic drugs that is based on a person's genes. Patients referred to his pharmacogenetics research clinic provide DNA samples that Dr. Mueller analyzes to determine how quickly or slowly they metabolize particular medications. He measures variations in two genes, known as CYP2D6 and CYP2C19, which make enzymes that break down many drugs often used to treat depression, obsessive-compulsive disorder and schizophrenia.

The difference between success and failure in benefiting from medication for a mental health problem may depend on how your liver breaks down a drug. People who metabolize a pharmaceutical more quickly than others, causing the substance to zoom through their systems, are less likely to respond to treatment, because the effects wear off too soon. Those who metabolize it too slowly are prone to side-effects, because the drug lingers in their bloodstreams. "A rapid metabolizer may need a higher dose to make the drug effective. A slow metabolizer may need a lower dose to reduce the side-effects," he says.

> Gene-guided dosing is an opportunity to leave behind the dark ages of prescribing by experimentation.

Dr. Mueller sees gene-guided dosing as an opportunity to leave behind the dark ages of prescribing by experimentation. The future of drug therapy may depend on advances in tailoring treatments to each person's DNA. "With traditional evidence-based medicine, you take 100 patients and decide what's best on average. With individualized medicine, you adjust the dose based on how an individual metabolizes the drug," says Dr. Mueller. "It's more accurate because you're treating the person rather than a group." ***hm***