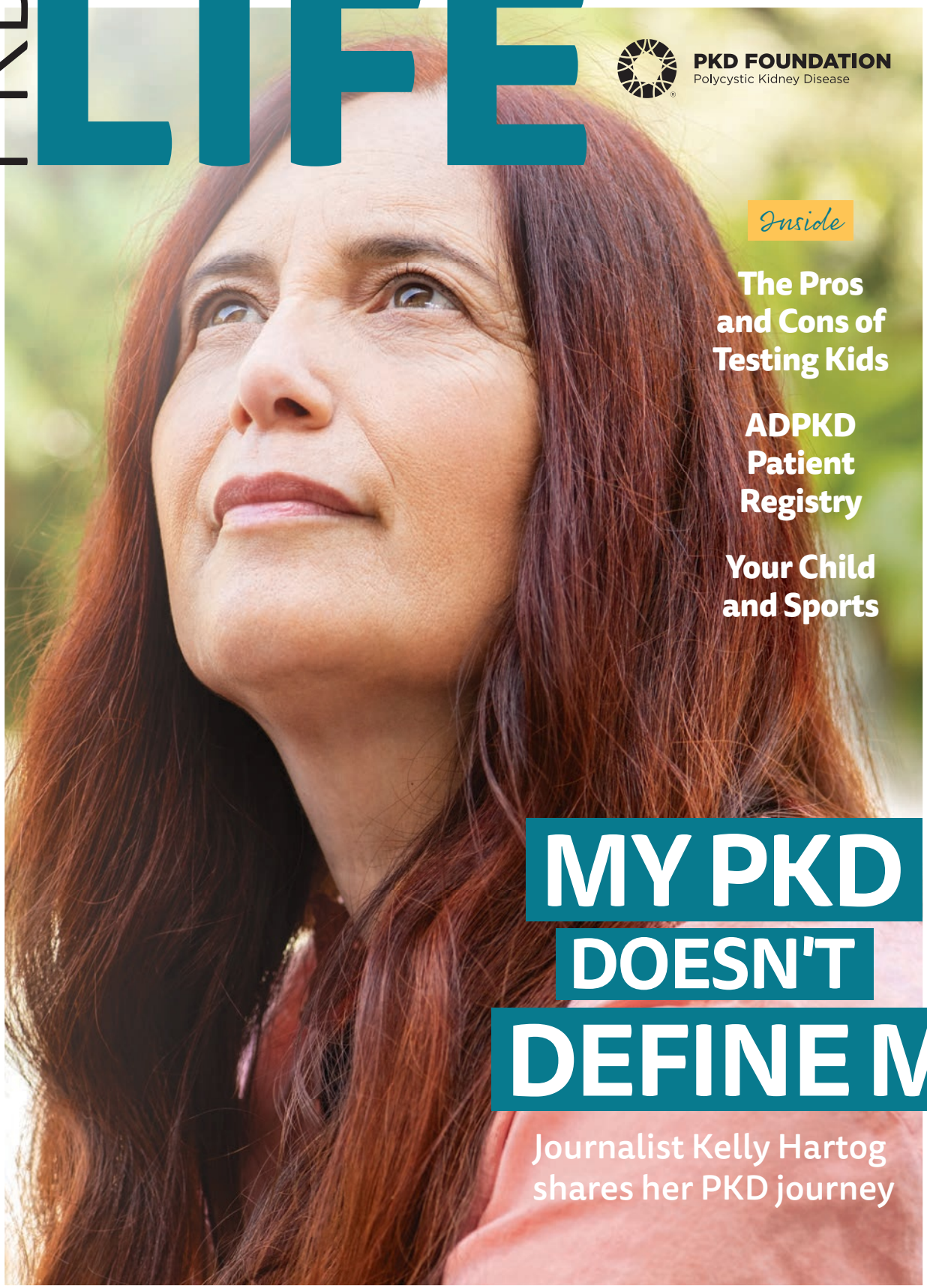
PKD LIFE

PKD FOUNDATION
Polycystic Kidney Disease



Inside

The Pros and Cons of Testing Kids

ADPKD Patient Registry

Your Child and Sports

MY PKD DOESN'T DEFINE ME

Journalist Kelly Hartog shares her PKD journey

WINTER 2020

New Treatments for PKD in Development

Clinical trials for several medications and lifestyle modifications are underway.

By Christina Frank

Prior to 2018, the only drugs that were available to people with PKD were those that controlled the symptoms and complications of the disease, such as high blood pressure and kidney stones. It was groundbreaking, therefore, when, in April of that year, tolvaptan became the first FDA-approved medication intended to stop the progression of PKD itself.

The approval of tolvaptan also marked the beginning of what Irina Barash, M.D., calls the "explosion" of new PKD treatments currently in the pipeline. Dr. Barash is an assistant professor of medicine at Weill Cornell Medical College and a nephrologist at the Susan R. Knafel Polycystic Kidney Disease Center at The Rogosin Institute in New York.

The reason it's taken so long for these drugs to emerge, says Dr. Barash, is because of the complexity of the disease. "The genes were identified in 1994, but it's taken time to understand the exact pathways that needed to be targeted," she says. "Also, the research technology has become so much more sophisticated since the genes were discovered."

It's hard to predict when new drugs will be on the market because there are several steps required before they are approved (*see sidebar*). Enrolling participants can take time, and some drugs may not make it from initial trials through to FDA approval. Here are the treatments currently being researched, and where they are in the pipeline.

BARDOXOLONE

Bardoxolone methyl belongs to a class of drugs called nuclear factor erythroid 2-related factor 2 (Nrf2) activators. Bardoxolone demonstrated improvement in kidney function, as compared with patient's baseline, in a phase 2 clinical study of ADPKD, and recently demonstrated positive interim data in a phase 3 study of patients with Alport syndrome, another inherited chronic kidney disease. The drug is currently in a phase 3 clinical trial for ADPKD called the FALCON study.

VENGLUSTAT

Venglustat belongs to a class of drugs known as glucosylceramide synthase (GCS) inhibitors. According to research done on mice, two types of glycosphingolipids are present in higher quantities in kidneys affected by PKD when compared with normal kidneys. Venglustat is thought to slow the growth of renal

THE 3 PHASES OF CLINICAL TRIALS

→ **Phase 1:** Tests the safety of the drug among 20 to 100 healthy volunteers and can take several months.

→ **Phase 2:** Tests the efficacy of the drug in several hundred volunteers and can last for two or more years. Usually, one group of patients receives the drug, and another group receives standard treatment or a placebo.

→ **Phase 3:** In this last stage before FDA approval, the drug is tested on several hundred to several thousand patients, and it can often last for five or more years.

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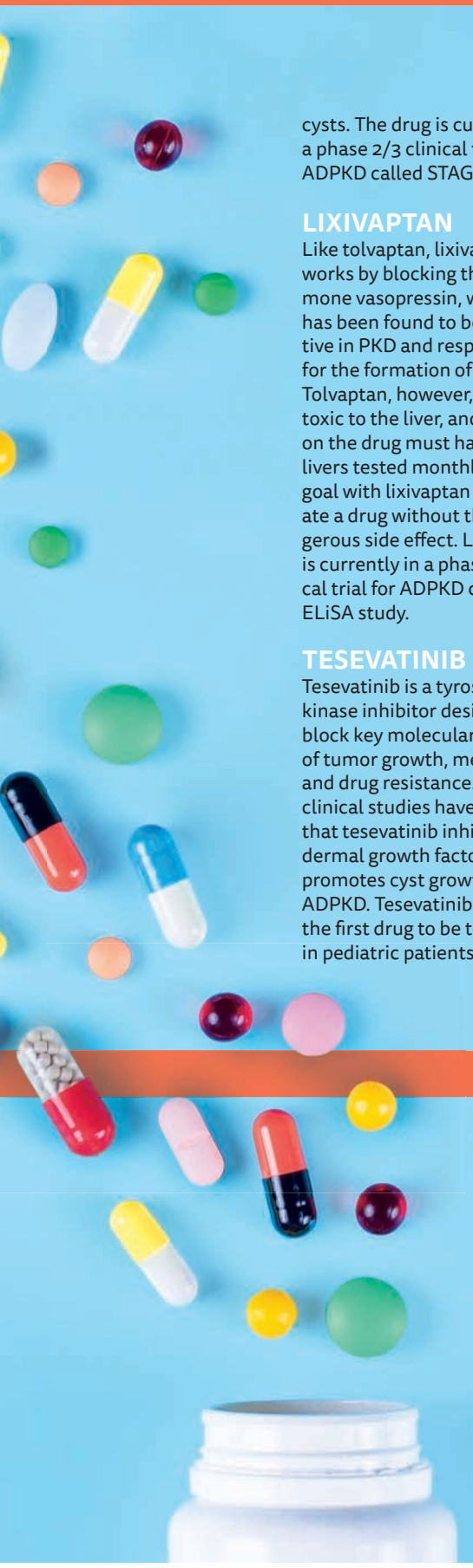

cysts. The drug is currently in a phase 2/3 clinical trial for ADPKD called STAGED-PKD.

LIXIVAPTAN

Like tolvaptan, lixivaptan works by blocking the hormone vasopressin, which has been found to be overactive in PKD and responsible for the formation of cysts. Tolvaptan, however, can be toxic to the liver, and people on the drug must have their livers tested monthly. The goal with lixivaptan is to create a drug without this dangerous side effect. Lixivaptan is currently in a phase 2 clinical trial for ADPKD called the ELiSA study.

TESEVATINIB

Tesevatinib is a tyrosine kinase inhibitor designed to block key molecular drivers of tumor growth, metastases and drug resistance. Early clinical studies have shown that tesevatinib inhibits epidermal growth factor, which promotes cyst growth in ADPKD. Tesevatinib is also the first drug to be tested in pediatric patients with ARPKD. The drug is currently in a phase 2 trial in adults and phase 1 trial in the pediatric population.

(It's important to note, says Dr. Barash, that drugs used for cancer treatment, such as tesevatinib, would be given at a fraction of a typical dose if used in PKD patients.)

RGLS4326

RGLS4326 is a targeted compound designed to inhibit microRNA-17, a molecular substance that is overactive in PKD cells. This is the only medication currently in the works that is given by injection; the rest are taken orally. Some preclinical studies with RGLS4326 have shown a reduction in kidney cyst formation, decreased cyst cell growth, and preserved kidney function in animals; the compound is being tested in a phase 1 clinical trial.

METABOLIC INTERVENTIONS

Drugs like pioglitazone and metformin, both FDA-approved treatments for Type 2 diabetes, are being "repurposed" for use in PKD in trials. It's been found that energy metabolism and glucose metabolic pathways in PKD cells are abnormal and can promote cell growth. The diabetes drugs can regulate these overactive cell metabolic pathways and have already been shown to slow disease progression in animals. Metformin and pioglitazone are currently in phase 2 trials.

LIFESTYLE MODIFICATIONS

Nondrug interventions that are being explored in PKD treatment are intermittent fasting and high water intake. Research has recently shown that inducing ketosis by fasting can inhibit cyst formation in preclinical models. High water intake can suppress the release of vasopressin, which would block the same pathway that tolvaptan and lixivaptan are targeting. Trials of high water intake, with individualized water amount prescriptions, are also underway.

A MULTIPLE DRUG APPROACH

Dr. Barash says because so many pathways are overactive and abnormal in PKD, it may be necessary to use a cocktail of therapies and lifestyle modifications. "This would allow us to target multiple pathways while using lower doses of each drug," she says.

People with PKD should stay informed about promising new therapies and not assume that all nephrologists know about them, says Dr. Barash. She also adds that "it's so important for patients to participate in clinical studies. Enrollment can be the slowest part of clinical trials." ●