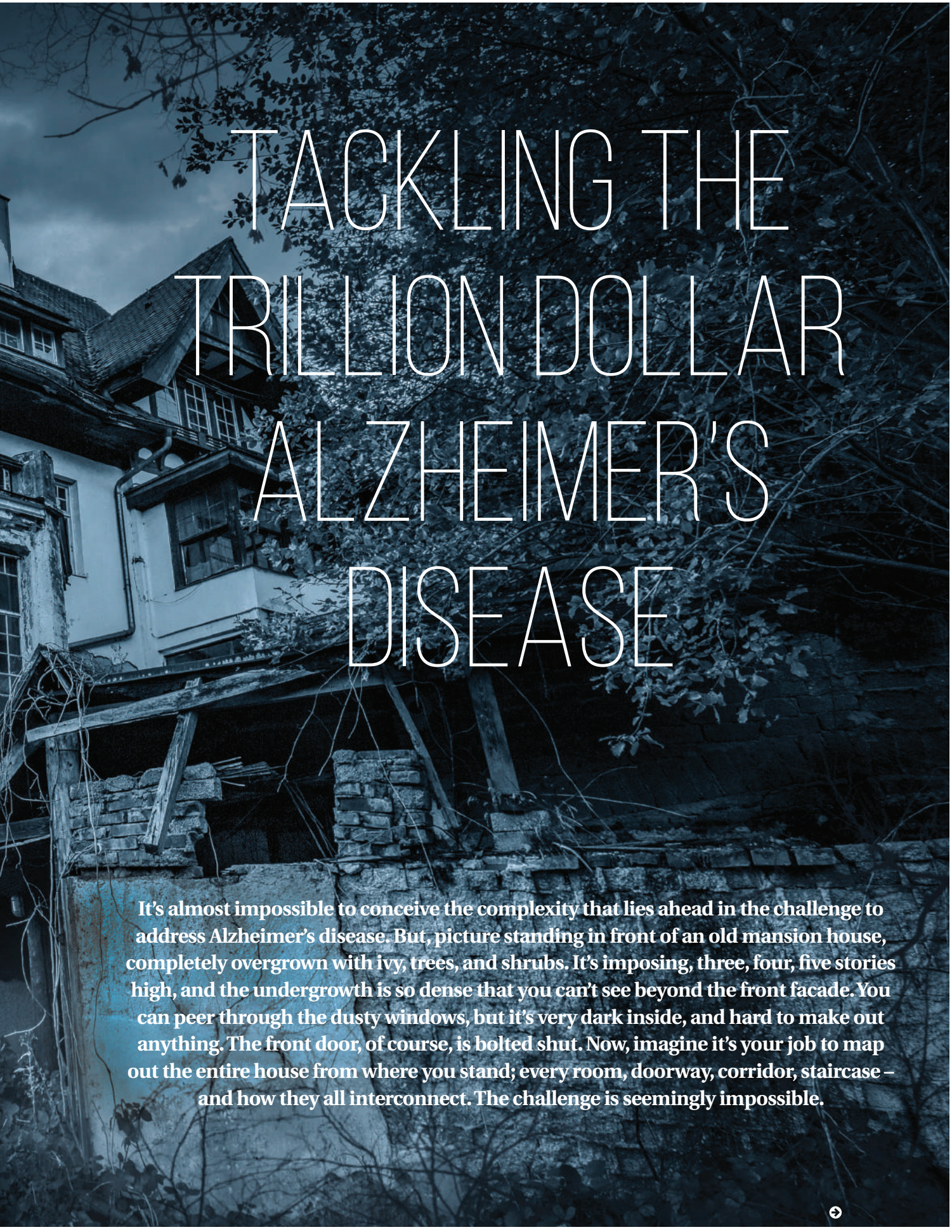

TACKLING THE TRILLION DOLLAR ALZHEIMER'S DISEASE

It's almost impossible to conceive the complexity that lies ahead in the challenge to address Alzheimer's disease. But, picture standing in front of an old mansion house, completely overgrown with ivy, trees, and shrubs. It's imposing, three, four, five stories high, and the undergrowth is so dense that you can't see beyond the front facade. You can peer through the dusty windows, but it's very dark inside, and hard to make out anything. The front door, of course, is bolted shut. Now, imagine it's your job to map out the entire house from where you stand; every room, doorway, corridor, staircase – and how they all interconnect. The challenge is seemingly impossible.

Like the mansion house, Alzheimer's disease is highly complex and poorly understood. Symptoms are no better defined than cognitive and functional impairment, which become more acute with disease progression; and the cause (other than in a few specific genetic cases) is broadly unknown. The leading theory is that Alzheimer's results from the deposition of amyloid plaques and tau neurofibrillary tangles (misfolded and tangled proteins) in the brain, together with a loss of brain mass. None of this is definitive as many individuals that do have such features, never develop disease.

Genetic variants of the APOE gene can offer greater insight into the risk of developing Alzheimer's. Indeed, the APOE E4 variant is recognised as the single most significant genetic risk factor for development of late onset disease. However, while 20-30% of people carry the APOE E4 variant, these individuals only account for up to 60% of all Alzheimer's cases; ie at least 40% of patients do not carry APOE E4.[1]

We do know is that the complexity of Alzheimer's stems from multiple risk factors based in genetics, lifestyle, age, and environment. As a result, there have been no new approved drug therapies since 2003; and until very recently clinical trial failure rates ran at 99.6%. Today over 50 million people worldwide are living with dementia, an umbrella definition covering more than 100 conditions that impair memory and cognition – of which Alzheimer's accounts for 50-70%. Best estimates set this figure to double every 20 years. The resulting global economic and healthcare financial burden of dementia broke the $1tn mark in 2018, and is estimated to reach $2tn per year by 2030.[2]

THE CHALLENGE AND FIRST STEPS TO TACKLING ALZHEIMER'S

Put simply, the challenge we face in treating Alzheimer's is that we have incomplete information. Firstly, about the nature of the disease, what causes it and how it progresses; and secondly about the patient, and their risk of developing disease in a largely unknown disease pathway.

To date, Alzheimer's – seen in patients as cognitive and functional impairment – has been defined by phenotypic symptoms, the deposition of amyloid plaques, loss of brain mass, plus the APOE gene variants that any individual may carry. As discussed, while these may be indicative of disease and the potential risk of developing disease, they have significant shortcomings.

Cytox is taking a far deeper look into the genetics behind Alzheimer's and provides non-invasive, risk assessment and patient stratification tools for the disease through a technique called a Polygenic Risk Score (PRS). PRS can provide a probability of a disease trait arising, based on multiple genetic loci and their associated disease-causing weights. The technique is not unique to Alzheimer's, indeed there is substantial research efforts in developing PRS approaches in coronary artery disease, type 2 diabetes, inflammatory bowel disease, breast cancer and glaucoma.

The Cytox approach to calculating a PRS in Alzheimer's uses its *geno*SCORE™ and *geno*TOR™ products that can detect and interpret around 500,000 single nucleotide polymorphisms (SNPs) linked to the disease. These SNPs may be either causative of or protective against Alzheimer's. As these tests are based on genetics, they can be carried out at any age, and before disease symptoms arise. The output from *geno*SCORE™ and *geno*TOR™ provide a risk score for developing disease, and indications on the timing of onset.

The age-old question remains however, "if there are no drugs to treat disease, how can knowing the risk and timing help, and does a patient want to know?" Interestingly, a recent UK report from Alzheimer's Research UK, and the pharmaceutical company MSD, explored public attitudes towards diagnostics in Alzheimer's. The report survey, based on interviews with over 2,000 adults, concluded that 74% of people said they would want to know if they had Alzheimer's before symptoms develop. This broke down to 38% who would want to know 15 years ahead of symptoms, and 33% two years ahead of symptoms. [3] And there is good reasoning for this.

The ability to predict these two parameters – risk of disease and timing of onset – are paramount in the future management of Alzheimer's. Early predictions – long before symptoms arise – allow for early interventions, which for now revolve around healthier lifestyle choices. These include improved diet and exercise, similar to those that negate cardiovascular disease and diabetes.

Secondly, and central to the development of new drugs, is the ability to identify patients at risk of developing disease, especially those with mild cognitive impairment (MCI) at risk of further substantial cognitive decline. The identification and recruitment of such patients to clinical trials increases the probability of observing the therapeutic efficacy of drugs being investigated. If efficacy can be shown, assuming it's safe, there is a pathway to getting regulatory approval and treating patients.

OPENING THE BOLTED DOOR

Despite the multi-trillion dollar societal burden that dementia and Alzheimer's pose, with hundreds of millions of people anticipated to need treatment in the coming years, poor success rates in Alzheimer's clinical trials have kept most pharma and biotech companies out of the field. And while recent news from Biogen that it is planning to seek FDA approval for its anti-amyloid drug, aducanumab, will likely create a new hope to the field, far more clinical trials in Alzheimer's disease are required before they are comparable to oncology – a disease in which major advances are coming through to patients. In 2015 there were 139 registered trials in Alzheimer's vs 4,976 trials in cancer.

Having a greater understanding of, and the ability to interpret, the complex genetics behind Alzheimer's is the first step to better characterising the disease. Furthermore, stratifying patients by their genetics is an essential step towards a more rational and targeted approach to drug development in the field. Cytox, through its polygenic risk score products – *geno*SCORE™ and *geno*TOR™ – is able to provide such insight.

And while this technology cannot provide all the answers from day one, it can unlock the door to the mansion house, provide the start of a floor plan and shine some light on where we should explore first.

References

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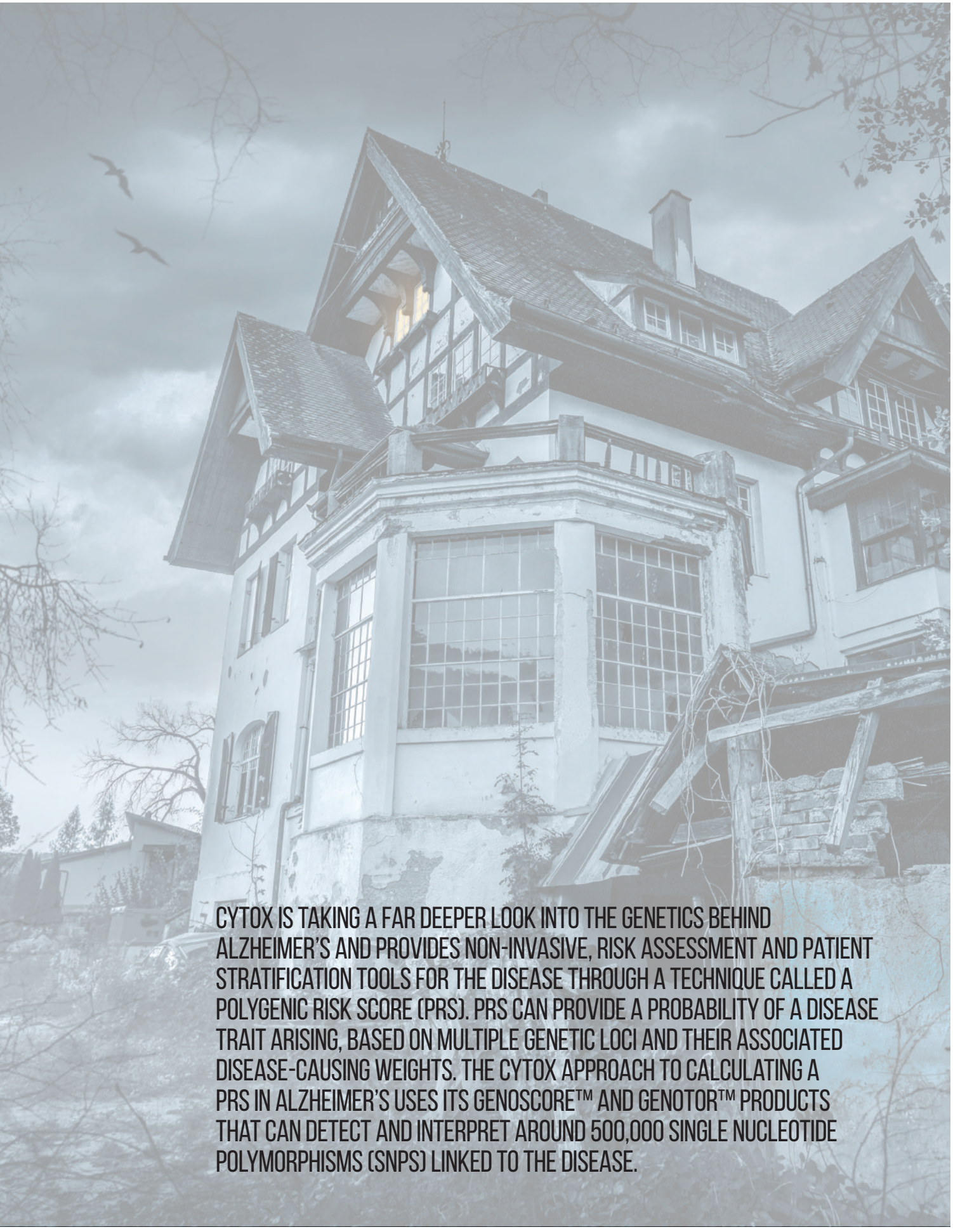
3. *Detecting and Diagnosing Alzheimer's Disease 2019 www.alzheimersresearchuk.org/wp-content/uploads/2019/12/1132267-Public-Perceptions-Report_v5.pdf*



CYTOX IS TAKING A FAR DEEPER LOOK INTO THE GENETICS BEHIND ALZHEIMER'S AND PROVIDES NON-INVASIVE, RISK ASSESSMENT AND PATIENT STRATIFICATION TOOLS FOR THE DISEASE THROUGH A TECHNIQUE CALLED A POLYGENIC RISK SCORE (PRS). PRS CAN PROVIDE A PROBABILITY OF A DISEASE TRAIT ARISING, BASED ON MULTIPLE GENETIC LOCI AND THEIR ASSOCIATED DISEASE-CAUSING WEIGHTS. THE CYTOX APPROACH TO CALCULATING A PRS IN ALZHEIMER'S USES ITS GENOSCORE™ AND GENOTOR™ PRODUCTS THAT CAN DETECT AND INTERPRET AROUND 500,000 SINGLE NUCLEOTIDE POLYMORPHISMS (SNPS) LINKED TO THE DISEASE.