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BIOMARKERS: AN INDISPENSIBLE ADDITION TO THE DRUG DEVELOPMENT TOOLKIT

EXAMINING THE POTENTIAL OF BIOMARKERS

Biomarkers are becoming an essential part of clinical development. In this white paper, Thomson Reuters explores the role of biomarkers as evaluative tools in improving clinical research and the challenges this presents. The potential of biomarkers to improve decision making, accelerate drug development and reduce development costs is discussed with insight from experts in industry and academia.



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Biomarkers are fast becoming an essential part of clinical development, not least because they offer a faster alternative to the conventional drug development approach and the promise of 'safer drugs, in greater numbers, approved more quickly'¹.

In recent times, the conventional approach has been courting failure more than it has success. The attrition rate for drugs in clinical development is high: the percentage of tested products entering phase I trials that eventually gain regulatory approval has been estimated at a paltry 8%².

Many of these failures happen late in clinical trials, with the consequence that expenditure in clinical drug development — already a mammoth effort requiring a huge amount of money, time, and patients — is increasing. One study calculated that the cost of developing a drug increased by over 50% between 2002 and 2007³.

Another consequence is that very few drugs are making it out of the clinical research pipeline. In 2007, the FDA approved just 17 new molecular entities and 2 biologic licenses, the lowest number since 1983⁴. Faced with these figures, there are growing concerns across the industry that pharmaceutical research is not bringing in sufficient gains for shareholders or for society⁵.

This is mainly due to a gap in the industry's ability to predict a drug candidate's performance early, and with a large degree of certainty. According to David Roblin, Vice President and Head of Clinical Development for Respiratory at Pfizer, predicting clinical efficacy is one of the "greatest bottlenecks in drug research and development"⁶.

The convention in clinical research has been to measure the performance of novel therapies using clinical outcomes. This approach is laborious, inexact and, as the US Food and Drug Administration (FDA) puts it, decades old. Many would agree when they say that novel therapies are not progressing through development and getting to patients as quickly as they could be⁷.

BIOMARKERS AS AN ESSENTIAL PART OF CLINICAL DEVELOPMENT

Biomarkers — a measure of a normal biological process in the body, a pathological process, or the response of the body to a therapy — may offer information about the mechanism of action of the drug, its efficacy, its safety and its metabolic profile.

There is wide consensus that biomarkers are and will be useful as evaluative tools in improving clinical research. Biomarkers feature heavily in the FDA's Critical Path Opportunities List for their potential to speed the development and approval of medical products⁸.

Because biomarkers can predict drug efficacy more quickly than conventional clinical endpoints, they hold the potential to substantially accelerate product development in certain disease

areas⁹. And because they help identify earlier those candidates that are likely to fail, they reduce drug development costs, giving life to the concept of ‘fail early, fail cheap’.

The FDA estimates that just a 10% improvement in the ability to predict drug failures before clinical trials could save US\$100 million in development costs per drug¹⁰. Biomarkers also offer the potential to inform treatment decisions and to bring personalized medicine into clinical practice.

“Biomarkers have certainly impacted our internal decision making on whether to move forward to the next phase of clinical development,” says James Weatherall, Research Clinical Scientist in Informatics at AstraZeneca. *“We wouldn’t make a decision to move to the next phase on biomarker evidence alone, but they can offer strong supporting evidence and in the future will be the key data in certain programs. They offer an objective, biological indicator, rather than just seeing whether the patients feel better.”*

“Biomarkers have certainly impacted on our internal decision making on whether to move forward to the next phase of clinical development”

James Weatherall, AstraZeneca

A BRIEF HISTORY OF BIOMARKERS

The idea of using biomarkers to detect disease and improve treatment goes back to the very beginnings of medical treatment. The practice of uroscopy — examining a patient’s urine for signs of disease — dates back to the 14th century or earlier, when practitioners would regularly inspect the color and sediment of their patient’s urine and make a diagnosis based on what they observed¹¹.

Today, your doctor may use spirometry to measure your lung function, take your blood pressure as a measure of your cardiovascular health, or test your blood glucose for diabetes. And not only are biomarkers useful at the ‘bedside’; biomarkers have already proved their worth at the ‘bench’ as well.

Philadelphia chromosome: In 1960, researchers discovered that some patients with chronic myelogenous leukemia (CML), a form of adult leukemia in which there is a proliferation of myeloid cells in the bone marrow, have a specific genetic change associated with their cancer, a shortened version of chromosome 22. This abnormality, known as the Philadelphia chromosome, is caused by a translocation between chromosomes 9 and 22. The consequence of this genetic swap is the creation of the BCR-ABL ‘oncogene’; this cancer-causing gene produces a protein with elevated tyrosine kinase activity that induces the onset of leukemia¹². Researchers were able to use the Philadelphia chromosome as a biomarker to indicate which patients would benefit from drug candidates (tyrosine-kinase inhibitors) specifically targeting the rogue protein. The end product was the drug imatinib (Gleevec), which decreases the proliferation of Philadelphia chromosome+ cells and slows the progression of the disease. As a postscript to this story,

researchers further found that specific mutations in the BCR–ABL gene were biomarkers that predicted resistance to imatinib, leading to the development of newer tyrosine-kinase inhibitors dasatinib and nilotinib.

HIV viral load: In the late 1980's, scientists discovered that HIV viral load could be used as a marker of disease progression, and subsequently, as a measure of antiretroviral treatment efficacy. Viral load was used to show that patients receiving combination therapy had a higher reduction in viral load than those on monotherapy, and was therefore more effective in slowing the progression of the disease. Eventually, the viral load biomarker was used in the development and assessment of Highly Active Antiretroviral Therapy (HAART) treatment regimens involving a combination of several drugs used by many people living with HIV today.

HER-2 gene and receptor: Probably the most famous biomarker in recent drug development history is the HER-2 gene and receptor, discovered in the mid 1980's. Between 20–30% of breast cancer patients show an over-expression of the HER-2 receptor on their cancer cells. Although this biomarker indicates a higher risk of adverse outcomes, it also gave clinicians a new target for novel therapies. The antibody trastuzumab (Herceptin) was developed to target HER-2 receptors in these 'overexpressing' patients, and successfully reduces the proliferation of cancer cells in many of these women.

PREVENTING DRUG DEVELOPMENT DISASTERS

The need for biomarkers to guide clinical research is perhaps best highlighted in the stories of recent drug development failures. Between 1995 and 2005, at least 34 drugs were withdrawn from the market, mainly as a result of hepatotoxic or cardiotoxic effects¹³. Many of us are familiar with the withdrawal in 2004 of the anti-inflammatory drug rofecoxib (Vioxx) due to concerns about its increased risk of heart attack and stroke, and more recently with the extremely serious adverse effects in the phase I clinical trial and subsequent failure of the monoclonal antibody, TGN1412.

TGN1412: This monoclonal antibody, produced by the firm TeGenero, was known as a 'superagonist', designed to directly stimulate an immune response. The therapeutic was originally intended to treat B cell chronic lymphocytic leukemia and rheumatoid arthritis, and had been tested pre-clinically with no toxic or pro-inflammatory effects¹⁴.

In 2006, six healthy male volunteers took part in a phase I clinical trial to test the safety of the candidate. Within 90 minutes of receiving the drug, all six men were experiencing the beginnings of a 'cytokine storm', a term that describes a cascade of proinflammatory cytokine release and the harmful

responses that they evoke, including fever, pain, and organ failure due to hypotension. Although all the men survived, they required weeks of hospitalization.

The cost of failures such as TGN1412 in terms of patient health and lost resources is huge. For many, the TGN1412 trial represented a failure in preclinical safety testing. It has been suggested that had procedures using safety biomarkers to guide dosing and predict the toxicity of this drug been used, the disaster may not have occurred¹⁵. As an indication of the subsequent recognition of the importance of biomarkers, in vitro procedures using safety biomarkers are now being applied to novel drugs that, like TGN1412, have the potential to act on the immune system.

BIOMARKERS TODAY

Today you “*would not even conceive*” of developing a new drug without simultaneously looking for biomarkers for efficacy, safety, and to measure the pharmacodynamics of the drug, says Dr Jeffrey Ross, Head of Pathology at the Albany Medical Center in New York and one of the researchers involved in the original work on HER-2.

The field of oncology is leading the way in the use of biomarkers in drug development. “*Clinical trials are designed upon biomarker assays,*” says Ross. “*If you look today, so many abstracts of phase II and III cancer trials talk about what biomarkers were selected. In vivo biomarkers, imaging biomarkers, blood and tissue based biomarkers, on and on and on. They are in every one.*”

One example of a biomarker in use in oncology is **circulating tumor cells (CTCs)**, a biomarker present in the blood of cancer patients. At the moment, CTCs are used in the development of anti-cancer drugs as an objective and direct measurement of the response of the cancer to a novel agent. “*It can give a pharmaceutical company a very early signal of efficacy,*” says Ross.

“*If you’re not knocking down the circulating tumor cells early in the trials, you may say, let’s save our money for the next agent.*” Although still in development, this biomarker holds further promise: the number of CTCs in the blood of patients with breast cancer, for example, is potentially a prognostic biomarker, and there is currently research ongoing to find out whether a decrease in CTCs associated with treatment can be used as a predictive biomarker of long-term benefit.

This use of biomarkers as alternatives to clinical endpoints in drug development, alongside an increased understanding of disease and the availability of funds for research into cancer, has meant that oncology has not experienced the downturn in drug development experienced by many other therapeutic areas. “*In fact, there has been acceleration in the development and introduction of new agents in the past ten years,*” says Ross.

“Clinical trials are designed upon biomarker assays”

Jeffrey Ross, Albany Medical Center

In particular, oncology has led the way in the use of genetic and proteomic biomarkers in drug development to predict an individual's response to treatment, starting with trastuzumab (Herceptin) in 1998 and imatinib (Glivec) in 2001.

"Candidate genes that determine responsiveness to a drug are important in biomarker studies," says David Roblin of Pfizer. "The old way that we used to do clinical trials was to enroll all patients with a given disease independent of gene or phenotypic makers. But if we can select a population with the particular gene which we believe to be important for response to a novel therapeutic, then we can run a smaller clinical trial to see whether it works or not."

James Weatherall of AstraZeneca agrees. *"What the regulatory bodies are asking for increasingly these days is not a one-size-fits-all medication, but one in which you can say what particular characteristics the patient would have to have for this medication to be most beneficial. If we can start to do that using genetic or protein markers in a rigorous way, then that's an incredibly powerful way to target the medication."*

The chemotherapy drug irinotecan (Camptosar) is one example of personalized medicine, using a biomarker to guide both clinical practice and subsequent clinical trials. Irinotecan is used to treat advanced colorectal cancer. Once administered, irinotecan is activated to the metabolite SN-38, and then eventually inactivated in the body by the UGT1A1 enzyme.

In 2005, the US Food and Drug Administration added a warning to the label of the drug, stating that patients homozygous for a particular a version of the UGT1A1 gene — the UGT1A1*28 allele, associated with decreased UGT1A1 enzyme activity — should be given a reduced dose. Because patients with this allele clear the drug less quickly from their body than the rest of the population, they effectively receive a greater exposure to the drug from the same dose. As a consequence, they are at higher risk of potentially life-threatening side effects such as neutropenia (a decrease in white blood cells) and diarrhea¹⁶.

The toxicity of irinotecan has long been a concern, and this biomarker now allows clinicians to better identify those patients who are at high risk of serious side-effects (about 10% of the population are homozygous for UGT1A1*28).

And while this pharmacogenomics information has helped improve the clinical use and efficacy of irinotecan, it has also fed back into the development of other drugs; almost immediately, this new understanding prompted the use of the UGT1A1 biomarker to guide other studies ongoing at the time, including several new irinotecan and oxaliplatin-based chemotherapy regimens¹⁷.

USING PRECLINICAL BIOMARKERS AS EVIDENCE OF EFFICACY

As mentioned above, biomarkers can accelerate research by substituting for clinical symptoms as a measure of efficacy. A clear example of this in preclinical research can be seen in the use of biomarkers for developing drugs for benign prostatic hyperplasia (BPH). Typically, the efficacy of drugs to treat BPH has been measured through the reduction of the patient's physical symptoms, like frequency of urination. However, there are other non-symptomatic markers, such as muscle tone in the prostate, which can be used to measure the effect of novel drugs pre-clinically.

"What you can do is look at animal models of increased prostate tone," says Pfizer's Roblin. "For instance, you could give adrenaline in an animal model to contract the prostate, then try out the novel drugs such as alpha-adrenoreceptor agonists to see if they dilate the prostate."

In this instance, biomarkers can also replace clinical symptoms when it comes to measuring drug safety. Alpha-adrenoreceptor agonists decrease blood pressure, and the goal is to develop a drug that is effective at a dose that does not decrease blood pressure to an unhealthy level.

"So using these models, you can not only look at prostate tone, but also look at blood pressure as a safety biomarker to find a dose that affects the prostate, but doesn't affect the blood pressure," says Roblin.

"That's a good example of where an efficacy biomarker plus a safety biomarker will define not just whether a drug will work, but also what kind of dose might be relevant in humans. It helps you understand the risk-benefit of the drug earlier. That's when the use of biomarkers really gets quite powerful."

"It helps you understand the risk benefit of the drug earlier. That's when the use of biomarkers really gets quite powerful"

David Roblin, Pfizer

IMPROVING EFFICACY IN CARDIOLOGY

Other biomarkers have arisen as a result of us better understanding the pathophysiology of disease, such as the role of inflammatory marker **C-reactive-protein (CRP)** in cardiovascular disease. CRP is released by inflamed atherosclerotic plaques in the arteries of individuals with coronary heart disease, and increased levels of CRP are associated with a greater risk of the plaque rupturing, forming a clot, and causing a heart attack.

CRP is currently being used as a biomarker to measure drug efficacy, in particular whether rosuvastatin (Crestor) reduces the risk of cardiovascular morbidity and mortality in apparently healthy individuals with low LDL-cholesterol levels but elevated CRP. Called the JUPITER study (Justification for the Use of Statins in Primary Prevention: an Intervention Trial Evaluating Rosuvastatin), it was halted in March 2008 due to firm evidence that the drug is indeed more beneficial than placebo and improves the prognosis of individuals with high CRP levels.

“CRP offers a new way of measuring the efficacy of statins,” says Dr Juan Carlos Kaski, Professor of Cardiovascular Science and Director of the Cardiovascular Biology Research Centre at St George’s University of London. “We have lots of studies showing that statin treatment improves survival in people with coronary artery disease. But now CRP is being proposed as a surrogate marker for efficacy.”

Kaski is also looking into another promising biomarker of cardiovascular risk called **neopterin**. Just as CRP is produced by inflamed atherosclerotic plaques at risk of rupture, neopterin is produced by activated macrophages that also play a role in this inflammatory process. Kaski and colleagues have found that circulating neopterin levels are higher in patients with acute coronary syndromes and may be a marker of coronary disease activity.

“Neopterin could also potentially be a marker of drug efficacy because if you reduce the number of active macrophages in the plaque or the circulation, the levels of neopterin also decrease,” says Kaski. Research is currently ongoing into this potential biomarker.

EARLY CONFIDENCE IN DRUG MECHANISMS

As the evidence demonstrates, disease-related biomarkers are clearly useful in clinical research. But there are less obvious biomarkers — those not necessarily linked to a specific disease — that are also significant, particularly in the early stages of drug development.

Mechanistic or ‘target’ biomarkers can be used in pre-clinical or phase I trials to measure the pharmacological effect of the drug, i.e. whether the drug interacts with its receptor, enzyme, or protein target, whether it is distributed to the site where it needs to act, whether there is some form of downstream pharmacology, and the dose ranges in which the drug is pharmacologically active. *“These types of biomarkers can be used to drive critical ‘go/no-go’ decisions in drug development,”* says Pfizer’s Roblin¹⁸.

An example of a mechanistic biomarker is **aldosterone**, a hormone produced by the adrenal cortex that acts on the kidneys to retain sodium and water. Drugs such as 5-HT4 receptor agonists (e.g. cisapride, mosapride), used in gastro-esophageal reflux disease (GERD), stimulate the secretion of aldosterone as a side-effect. Although aldosterone is not linked to GERD (and can’t be used as a biomarker of the disease), the hormone can be used as a mechanistic biomarker in drug development to assess whether novel 5-HT4 agonists in development have a pharmacological effect¹⁹.

“Obtaining this information is an overarching goal in drug development,” says Roblin. *“The earlier you can demonstrate these points, the better. If you have a marker of the mechanism that shows some sort of downstream pharmacological effect, you can advance the drug with much more confidence.”*

Aldosterone can also be used to assess at what doses the 5-HT4 agonists have an effect. *“What this means from a trial perspective,”* says Roblin, *“is that instead of testing a ten-fold dose range, you could test in perhaps just a couple of doses.”*

“These types of biomarkers can be used to drive critical ‘go/no go’ decision in drug development”

David Roblin, Pfizer

Another example of a biomarker used in proof of mechanism, this time in oncology, is pRB phosphorylation. pRB (retinoblastoma protein) is a tumor suppressor protein produced by the RB gene that is dysfunctional in many types of cancer. A reduced level of phosphorylation of this protein can indicate whether certain types of oncology drugs are effective.

AstraZeneca recently used pRB phosphorylation as a biomarker in a phase I trial of novel oncology drug AZD5438, designed to target cancerous tumors. Biopsies from the inside of the participants' mouths were analyzed for levels of pRB phosphorylation at different doses. The biomarker helped AstraZeneca decide not to move forward with AZD5438.

"We looked at safety versus efficacy and saw that there wasn't a happy medium," says AstraZeneca's Weatherall. "We realized that the dose we needed to have a sufficient mechanistic effect was not tolerable by the patient." Without a biomarker, this drug may possibly have made it to phase II trials, says Weatherall. "But this information allowed us to make a 'kill' decision for that program, because clearly the drug wasn't having the mechanistic effects at the dose that we desired."

"We looked at safety versus efficacy and saw that there wasn't a happy medium"

James Weatherall, AstraZeneca

FUTURE CHALLENGES: DISCOVERING NEW BIOMARKERS

One of the major challenges to innovation is our ability to discover new biomarkers. Part of the answer lies in gaining a better understanding of the pathophysiology of disease, thereby uncovering potential drug targets and biomarkers in the disease pathway.

"The industry wouldn't have over 80% attrition of novel therapies in phase 2 if we understood human disease," says Roblin from Pfizer. "The fundamental issue we have to deal with, both with target selection and developing better biomarkers, is a better understanding of pathophysiology."

The clinical need is huge, not least in diseases like chronic obstructive pulmonary disease (COPD), an illness about which we know very little. *"COPD has very few markers to indicate severity and disease progression,"* says Dr Trevor Hansel, Medical Director of the National Heart & Lung Institute Clinical Studies Unit in London.

"In asthma at least we have biomarkers like sputum eosinophils and allergen challenges, and we're able to do short term, proof of concept drug studies. But in COPD, we don't have equivalent biomarkers. So there's the risk that you do harm because you can't measure safety with biomarkers beforehand," says Hansel. But the major risk, he says, is committing to a large phase III study without proof of drug efficacy. *"Finding biomarkers to improve our assessment of efficacy and safety in small numbers of patients is where all the initiatives are directed at."*

In 2006, GSK launched the ECLIPSE project, a three-year study following the progression of COPD in over 2000 patients. The study is actively looking for biomarkers that may help to improve our ability to diagnose COPD, define its severity and predict its progression over time, and ones that can eventually be used in drug development.

“We don’t currently have many good biomarkers in respiratory medicine. The reality is, there’s a disconnect between the science, and getting that science into the clinical arena,” says Hansel.

This need for biomarkers is not just restricted to respiratory medicine. *“There are substantial needs in cardiology,”* says Kaski of St George’s University of London. *“We need to develop drugs in practically every area, from congenital disease to hypertension, stroke and myocardial infarction. The difficulty is in understanding the disease process, and identifying some of the players in these pathways that will play a role in identifying whether your treatment is useful or not.”*

INVESTING IN ‘OMICS’

Estimates show the total number of biomarkers of interest at about 1,133,00020 — a potentially overwhelming number. However, many pharmaceutical companies have begun to invest in ‘omics’ — genomics, proteomics, metabonomics — to begin to sort through this mountain of molecules and characterize biomarkers based on a molecular understanding of disease.

The ‘omics’ approach enables the detection of small changes in tissue composition through protein profiling technologies such as mass spectrometry and gel electrophoresis. Essentially, it is about capturing a molecular profile from a clinical sample and converting this into information about a clinical condition — for example the stage of disease or what players are involved in the disease pathways.

‘Omic’ approaches are already beginning to divide diseases into new subtypes, previously unrecognized by traditional disease classification methods that relied on symptoms and observations of pathology. *“With this approach, we can start thinking about disease in a new way. We will be able to look at diseases and categorize them based on biochemical or physiological findings, rather than just on symptoms,”* says Roblin.

Schizophrenia is an example of a disease that many believe could benefit from an ‘omics’ approach because it offers the chance of finding a biological basis for the disease and biomarkers involved in the disease pathway. *“At the moment, schizophrenia is an accumulation of symptoms. What we haven’t done is describe the disease based on the molecular or genetic or phenotypic error that’s occurring in that particular patient,”* says Roblin.

“We will be able to look at diseases and categorize them based on biochemical or physiological findings, rather than just on symptoms”

David Roblin, Pfizer

By finding molecular biomarkers of the disease, diagnosis could be improved and could reveal new information about the disease. So if you determine that schizophrenia is in fact five pathophysiological processes, by measuring biochemistry, imaging, or perhaps genotypic biomarkers, then you would have a better chance in developing drugs for schizophrenia 'type A', for example.

"It may give the industry an opportunity to advance drugs that we may not have in the past, because before we may not have seen a very good effect. But if you suddenly know that it's patients with this gene defect or this biochemical abnormality or this imaging finding that show a strong effect, then suddenly you can target these patients," says Roblin.

TRANSLATIONAL MEDICINE

The ultimate vision is to have access to biomarkers in all therapeutic fields. *"It certainly is a dream,"* says Ross. *"I don't know whether that's going to happen for all diseases... but we're discovering new ones all the time."*

"You need industry, academia and clinicians working together," says Hansel, *"which means changing the way we approach the development of new drugs."* Already consortiums — such as the Innovative Medicines Initiative, the National Institutes of Health Biomarker Consortium, and the Pharmaceutical Research and Manufacturers of America Biomarker Consortium — are pooling information on biomarkers and other disease-related information so that clinical trials more often provide clear and unequivocal results²¹.

"The issues are common across industry and academia," says Roblin. *"The opportunity to work together to deal with bottlenecks in R&D including discovering, developing and validating biomarkers is very attractive."*

The challenge is great, but so is the reward. *"Biomarkers could have such a huge impact, because you could reduce the time of your trials and improve internal decision making. That means that everybody wins,"* says James Weatherall of AstraZeneca. *"The pharmaceutical companies get to conduct their drug development programs in a much more expedited fashion and get to the business of getting the drug on to the market, and the patients get the medicines they need more quickly as well."*

"You need industry, academia and clinicians working together"
Trevor Hansel, National Heart & Lung Institute Clinical Studies Unit

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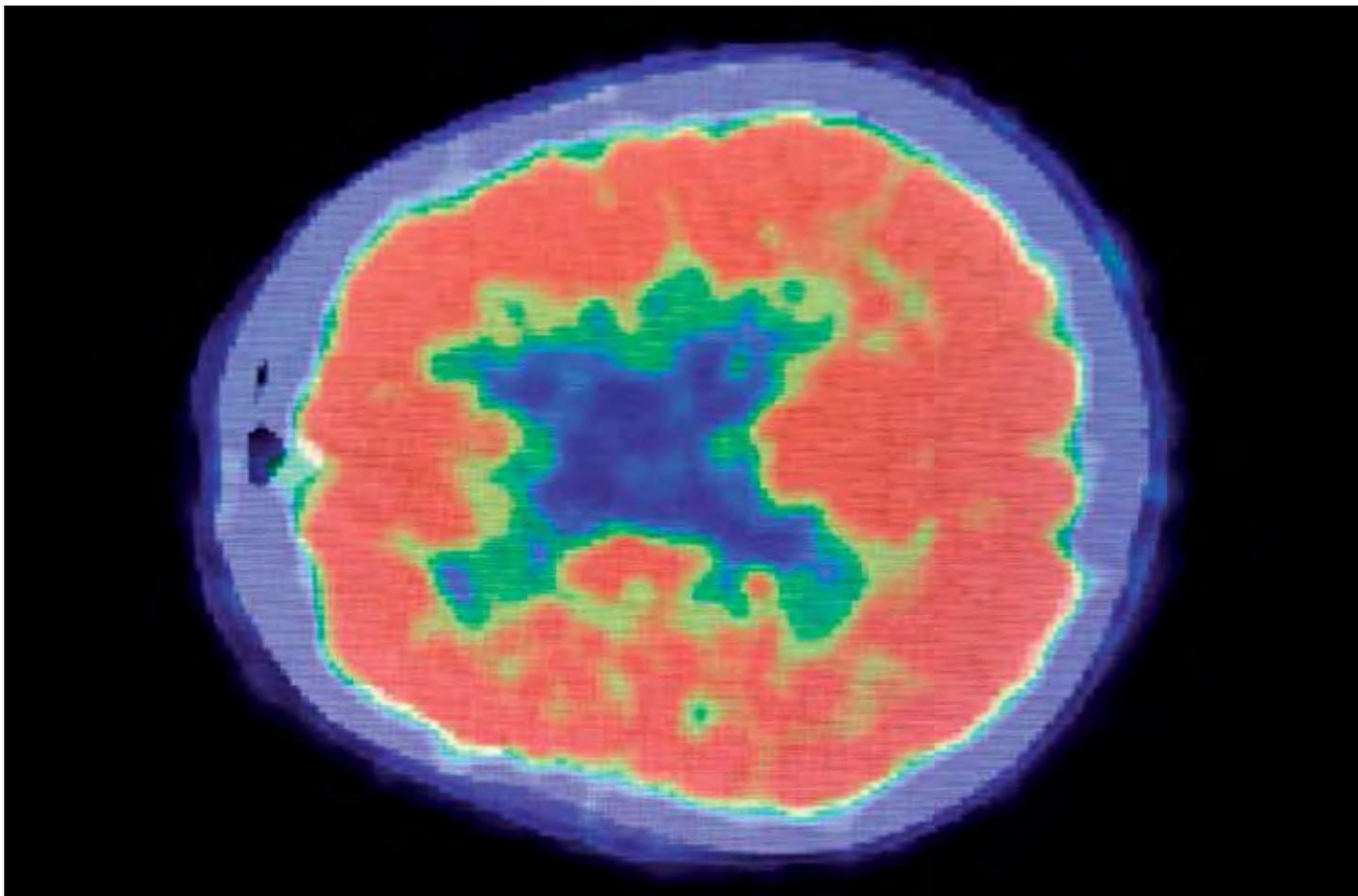


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