THE PROMISE OF IMAGING BIOMARKERS

In this white paper, Thomson Reuters provides a snapshot of the imaging biomarkers at use in research and development, and the clinic; examines key technical and commercialization challenges; and identifies promising avenues for progress in the field with insight from experts from industry and academia.

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Biochemical and molecular markers have revolutionized medicine and drug development in recent decades, giving clinicians and researchers the opportunity to infer biological states in patients and in response to drug interventions. For example, the blood of HIV patients can be tested for its viral load to assess the course of their disease, as well as providing a surrogate endpoint for trials of anti-HIV drugs.

Now imaging biomarkers are coming into their own, offering earlier detection of some diseases than molecular markers and enabling practitioners to see into the body without the need for invasive procedures — of great benefit to clinicians and patients. They are also allowing researchers to see for the first time how their candidate drugs are behaving in great detail, from determining the percentage of receptors occupied by a drug on target cells to looking at a drug's ability to cross the blood/brain barrier. This in turn can save time and money at the drug development lab bench. It is no exaggeration to say that imaging biomarkers are promising to revolutionize basic research, drug development, and treatment.

The use of imaging biomarkers has progressed steadily for more than a decade, exemplified by using magnetic resonance imaging (MRI) in assessing treatment for multiple sclerosis. "What we have done in the last 10 years was to use [MRI] as a primary endpoint to demonstrate and validate the capacity of interferon as a treatment of patients," says Salvador Pedraza, Director of Care, Imaging Diagnostics Clinic, Hospital Universitari Josep Trueta.[1]

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Salvador Pedraza, Hospital Universitari Josep Trueta

Many hundreds of imaging biomarkers are already used in drug discovery and development as well as in the clinic. At Pfizer, for example, imaging-based endpoints are widely used in translational oncology research.[2] Within the last two years, GlaxoSmithKline (GSK) has established a clinical imaging center in London which, for example, uses imaging biomarkers to help determine dosing for central nervous system (CNS) drugs. Merck also has a pre-clinical imaging center.

The promise of imaging-based biomarkers to streamline drug discovery and development and healthcare is enormous. Yet we are still at the beginning of imaging biomarkers' rise to prominence. Recent advances in imaging technology and the ability of imaging-based biomarkers to provide often-unobtainable guiding information has prompted a dizzying surge in imaging biomarker research and development (R&D). A recent PubMed™ search on "imaging"' returned half a million items and a search for "imaging biomarkers" returned around 1,000 citations from just the first nine months of 2009.[3]

IMAGING TECHNOLOGIES

Biomarkers are measures of a normal biological process in the body, a pathological process, or the response of the body to a therapy. Imaging-based biomarkers employ a variety of technologies to capture images of anatomical and physiological changes in the body.

X-Ray: In clinical settings, x-rays are emitted towards the body, passing through it and creating an image recorded onto film, or more recently, digitally. X-ray technology has been in use for over 100 years and has served to identify structural markers in biomedicine for almost as long.

Computed Tomography (CT): Sometimes also called computed axial tomography (CAT scan), in this technique x-rays are used to take a series of 2-dimensional images which are then digitally converted to a 3-dimensional image. CT was introduced during the 1970s and its use has expanded widely.

Positron Emission Tomography (PET): A short-lived radioactive tracer isotope, fluorine(18F) for example, is injected into the body, usually attached to a probe molecule that accumulates in the tissue of interest. The isotope emits a positron (an anti-electron) which travels a short distance before colliding with an electron. The collision annihilates the two particles and emits two gamma rays travelling in opposite directions which are detected by a scanner. Computerized tomography assembles a 3-dimensional image of the area of interest. The first PET machines for use in humans were introduced in early 1970s.

Single Photon Emission Computed Tomography (SPECT): A gamma ray-emitting tracer isotope is introduced into the body and a gamma camera is used to collect multiple 2-dimensional images which are later assembled into a 3-dimensional image. SPECT is significantly less expensive than PET in part because the tracer isotopes are longer-lived and less costly. However SPECT's resolution is also lower than PET.

Magnetic Resonance Imaging (MRI): No ionizing radiation is used. Instead, the subject is placed in a powerful magnetic field which aligns the nuclear magnetic field of atoms, usually hydrogen atoms in the body's water. Radio frequency signals are used to alter the atoms' magnetic alignment and the resulting signal is detected by scanners. MRI is better at distinguishing soft tissues than tomography. The first MR image was published in 1973, the first cross-sectional image of a living mouse in 1974, and the first studies performed on humans were published in 1977.

In addition, optical imaging is frequently used in drug discovery and pre-clinical animal research, and is increasingly used in the clinic for humans, for example with optical CT scanning. Ultrasound (US) is also often used in the clinic and recently has been explored as a method to deliver drugs.

IMAGING IN R&D

Imaging technologies and biomarkers — x-rays, for instance — have been used in the clinic for years but the push into drug R&D is more recent. "That's a trend of the last six or seven years. It used to be just exploratory activity but now it's increasingly tied to development and partially used to make go/no-go development decisions," says imaging authority Oliver Steinbach, the Head of the Bio-Molecular Engineering Department at Philips Research Laboratories.[4]

The type of imaging biomarker used depends on the drug development phase. Optical methods such as microscopy and high content screening, where fluorescent tags or antibodies are used to visualize proteins, dominate early discovery work and are used in assessing target expression and function as well as compound screening and lead discovery. Pre-clinical animal studies - focused more on efficacy, toxicity, pharmacokinetics and pharmacodynamics - rely more on PET, SPECT, MRI along with optical methods.

Translational research is one area receiving a huge boost from imaging. "Both MRI and PET combined with CT provide very good imaging biomarkers to assess response to treatment. That has changed the way development occurs because in the past it was necessary to sacrifice the animals to establish proof of response [to treatment]," says Ignasi Carrió MD, Director of the Nuclear Medicine Department at Barcelona's Hospital Sant Pau, and Editor-in-Chief of the European Journal of Nuclear Medicine & Molecular Imaging. "Now, imaging biomarkers can be used over time without having to sacrifice the animal."

This growing ability to use imaging biomarkers to conduct longitudinal studies in the same animal is reducing cost, saving time, providing better progression data, and bolstering confidence in results. Subtler therapeutic effects and negative toxicity signals are often detected earlier and more easily, and laborious biochemical assays can be avoided.

Recognizing the power of imaging biomarkers to provide critical molecular and anatomical data, major pharmaceutical companies have begun to use imaging more aggressively. The GSK Clinical Imaging Centre is one such effort where imaging, mostly molecular, is being put to use in CNS and oncology research.

"We use mainly PET in the CNS to determine target pharmacokinetics, to look at drugs binding to their target and look at dosages at which drugs occupy the target at an efficacious level and use these data to develop dose regimens for phase I and II trials," says Eugenii Rabiner, Director of Clinical Imaging Applications at the GSK Clinical Imaging Centre.[5]

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"Obviously in the CNS imaging has a big role because you can't really access it with anything else. In areas like oncology you can go in and take biopsies; that's not feasible in CNS. You can get quantitative measurements, such as the percentage of receptor occupancy. If you're looking [at a drug's] brain penetration, you're getting a ratio between [drug levels in the] brain and blood. I think we are reasonably confident these measures correspond to reality," says Rabiner.

He gives the example of antipsychotic medication that targets the D2 dopamine receptor. "It's been generally accepted that for acute antipsychotic effect you need to get your D2 occupancy up above 65% and when you go above 80% you start getting side effects," says Rabiner. "If you are developing a compound which works by blocking the D2 receptors, you can go in and look at its occupancy at D2 and if you're in that range with your compound you know you're likely to have an effect without too many adverse events."

The use of other forms of imaging in drug development are more experimental. For example, functional MRI (fMRI), a specialized form of MRI that is used to determine neural activity by visualizing blood flow, is often used in academic research but has so far proved less useful in drug development, according to Rabiner. "It's still somewhat exploratory. Potentially it could be very useful but there are many questions about whether you can equate changes in an fMRI signal reliably to drug effect."

And few imaging biomarkers are used in late-stage clinical trials because it is harder to verify the links between the biomarkers and clinical response. Establishing a validated imaging-based surrogate endpoint is even more difficult.

Most examples of use in late-stage trials are in oncology and neurology. For example, the size of a tumor can serve as an imaging biomarker using MRI, CT or even ultrasound. PET and SPECT can be used to assess tumor metabolism and proliferation. Tumor angiogenesis, detected with MRI or sometimes ultrasound, is also a kind of imaging biomarker. And there are MRI protocols to assess lesion sites in multiple sclerosis.[6]

IMAGING IN THE CLINIC

One concrete example of an imaging biomarker in the clinic is the use of the fluorine isotope combined with the glucose analog fludeoxyglucose ((18F)FDG) in PET/CT to diagnose tumor recurrence in colon cancer. Serving as a surrogate of glucose metabolism, PET/CT imaging "is crucial in [detecting colon cancer recurrence] compared to biochemical markers because you need localization of the recurrence to offer surgery, the only curative treatment in these type of patients," says Carrió.[7]

No biomarker should be used alone, emphasizes Carrió: "In real life you must use a combination of biomarkers. In the particular case of suspected recurrence of colon cancer, you must use at least two biomarkers, including one non-imaging biomarker like GUCY2C (guanylate cyclase 2C)."

"In real life you must use a combination of biomarkers." **Ignasi Carrió MD, Nuclear Medicine Department Hospital Sant Pau Barcelona**

And combining technologies is becoming more popular. "You could say multimode modality is the emerging trend. We don't even call combinations of PET and CT or SPECT and CT multi-modality anymore, it has become so standard," says Steinbach.[8]

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"PET/CT is the state of the art in clinical oncology," agrees Carrió. "The next development in the industry will put into the market hybrid MRI/PET systems trying to combine the best part of MRI and PET and in areas where MRI is better than CT, say when soft tissue contrast is necessary or in the breast or in the brain."

And new multi-mode approaches will emerge, such as "ultrasound and MRI and SPECT using dual isotopes," says Steinbach.

Also looking to the future, Steinbach says that improvements could be made in offering clinicians more molecular imaging biomarkers. Most imaging techniques are used purely to identify anatomical changes, he says, but recent advances in using molecular biomarkers for imaging are enabling researchers and clinicians to more directly detect the effect of a drug.

"More specific agents and tracers not only show anatomical support in [for example] perfusion imaging but also allow you to specifically detect, quantify and locate pathological areas. In the experimental field we have an enormous wealth of tracers, optical tracers, radioactive tracers etc., but in the human field it is somewhat limited. I think those will become increasingly important," says Steinbach.

REMAINING CHALLENGES

Despite the promise, imaging biomarkers face many hurdles before they can be widely adopted, from standardization and a regulatory policy in its infancy, to finding ways to store and analyze the resulting plethora of information. Fortunately, both users and providers are well aware of the issues and many groups are tackling them.

"Technology is actually not the point anymore. It's more like how do you handle, store, retrieve, and analyze the enormous amount of data generated by these technologies," says Steinbach.

A good though extreme example of the staggering data volume challenge is Eugene Myers' work imaging mice brains. Myers, a Howard Hughes Medical Institute investigator, is a co-inventor of the BLAST algorithm used in DNA sequencing.

"[It is] clear that moving the data is a real bottleneck," **Eugene Myers, Howard Hughes Medical Institute**

He is currently wading into a data flood, tackling the 4.2 trillion voxels (or 3-dimensional pixels) that imaging a single mouse's brain will produce in just one week.[9]

"[It is] clear that moving the data is a real bottleneck," says Myers. "Just to do a compute on this thing, you've got to get 4.2 terabytes out of the disk system to the various processors. You have to move huge volumes [of data] so distributed file systems are very important to use."

But standardization is perhaps the biggest challenge in this budding field. Differences in vendor equipment and user practices as well as varying ideas about what to measure — and how to measure it — are all important standardization issues.[10]

"I think quantification is still something that's in its infancy in medical imaging — even the question of what to actually quantify." **Oliver Steinbach, Philips Research Laboratories**

"How much of the biomarker is there? How big is the change? If you want to compare healthy versus disease, you need to have a relative quantification," says Steinbach. "I think quantification is still something that's in its infancy in medical imaging — even the question of what to actually quantify. If you measure physiological activity, for instance, with a tracer, is it disintegrations per minute? Or is it disintegrations per hour?"

These questions are less an impediment to early discovery work, but become critical as you move to the clinic. Several organizations are working to solve them. The Radiological Society of North America has a working group on the topic and the Biomarkers Consortium, a project overseen by the Foundation of the National Institutes of Health in the United States, has specific projects underway.[11]

One project is attempting to standardize dynamic contrast MRI, which is used in cancer to measure blood flow. Using prostate cancer as the model, the plan is to gather data across 10 or more clinical sites and create sets of benchmark data points that can be used to create and then validate a standardized model.[12]

A similar project is standardizing carotid MRI, which measures atherosclerotic plaque size to distinguish vulnerable from stable plaque. Involving 10–15 imaging centers, the consortium is going to pay for 80 patients to be measured using different scanning techniques across the sites and document the variability between the sites and scanners.

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Ease of use is another pressing need, says GSK's Rabiner. "Complicated measurements work well in the hands of the people that understand them but are extremely difficult to standardize and to incorporate into day-to-day work. At the end of the day the [skills] remain confined to a few centers of excellence but are never used as a standard biomarker for patient management."

Pedraza agrees, "[We need] to validate systems to obtain automatic quantification of parameters. At the moment, most imaging biomarkers are determined by experts and so are good

but time-consuming. We need to validate an automatic way to obtain the quantification [so fewer expert personnel will be needed]."

APPLYING IMAGING BIOMARKERS

The cost of new technology is often an issue and imaging biomarkers are no exception. Much of the big pharma community has invested in dedicated imaging groups while many smaller companies are doing so "virtually," by using the equipment of other companies.

Rabiner admits that the GSK Clinical Imaging Centre is a significant investment. "We will see the debate about whether this should be done in house or externalized. There are arguments for both ways. There are many pharma looking to see how we get on; have we provided enough return to GSK to justify this large investment? If [yes] then there might be a rush by pharma to build up their own centers. If not they may decide to externalize."

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Persuading those who pay for healthcare, such as insurance companies and government agencies, is another hurdle. "If we are moving to a kind of healthcare scenario where you have a certain budget per patient to cure or manage a disease then the budget must be used as effectively as possible," says Steinbach.

"It's realistic that powerful new generation therapies for cancer or Alzheimer's could cost US$50,000 per patient per year. Using an inherently more expensive imaging procedure for the planning and guidance of therapy becomes financially attractive. It's clear in oncology you will see effectiveness of a tumor therapy on a molecular level [with biomarkers] much earlier than you see the real shrinkage of the tumor. Seeing a tumor shrinking with nuclear magnetic resonance will take weeks; whereas to see a change in its metabolism with PET will probably take a few days. That's where the power of imaging is."

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Regulatory agencies are less of a stumbling block. Many are enthusiastically embracing and promoting the development of imaging biomarkers, as exemplified by the U.S. Food and Drug Administration's strong support in its 2004 Critical Path Initiative.[13]

But regulatory agencies are understandably cautious and may move more slowly than researchers would like.

Carrió says, "Agencies collect the evidence after new imaging technologies have arrived. It is important to collect the evidence and to make the evidence public in a short time period to keep up with development in the field. It can take 5–10 years for health technology agencies to deal with evidence and in the meantime other technologies are already there."

DIGGING OUT BIOMARKER DATA

The surge in biomarker development broadly and imaging biomarkers in particular has complicated researchers' efforts to track progress in the field.

"Think about a protein, EGFR2 for example. How many synonyms does it have, 15 or 20? Every biologist, every scientist uses their preferred synonym for it and they publish using those different names," says Colin Williams, Director, Product Strategy, Thomson Reuters Life Sciences.

Thomson Reuters is expert at assembling specialized databases to help researchers and clinicians quickly find the information they need with sufficient detail to enhance their work. Thomson Reuters recently launched *BIOMARKERcenter*™, a comprehensive database of biomarkers covering all key biomarker uses at every stage of drug R&D. "This will help researchers spend more time at the bench conducting experiments and less time at their computers finding the information they need to drive successful therapy development" says Williams, emphasizing just how much time scientists could save using the database.

"One of the challenges from an information perspective is there is no hierarchical ontology management system for all of this information. You've got things like the MeSH (Medical Subject Headings) ontology tree for medical terms, but there's nothing for imaging biomarkers at all," **Colin Williams, Thomson Reuters**

Building on that success, Thomson Reuters is adding imaging biomarkers to the database. As Williams explains, creating the imaging biomarker database was no small task: "One of the challenges from an information perspective is there is no hierarchical ontology management system for all of this information. You've got things like the MeSH (Medical Subject Headings) ontology tree for medical terms, but there's nothing for imaging biomarkers at all."[14]

"There's a framework in place for molecular biomarkers, but we came up against a big barrier with imaging biomarkers and had to invest a lot of time in creating a standardized terminology," says Williams. "It comes back to looking at an article and saying, what's the author talking about here? Let's group this into a technique using standardized terminology so people can find all of the uses that are relevant."

In doing this, Thomson Reuters, with the guidance of key imaging biomarker experts, had to create standard indexing guidelines, ontologies, and vocabularies before assembling and organizing the material. This massive effort involved Thomson Reuters' scientists poring over a wide range of source material, from the scientific literature and conferences to press releases. They scoured the literature, asking themselves, "What is this paper actually about, what are the biomarkers being used for? Is it for diagnosis, prognosis or stratifying a patient population? What techniques have been used to find this biomarker? Those layers of complexity are [searchable] in the database," says Williams.

Williams says *BIOMARKERcenter*, currently heavily comprised of molecular biomarkers, shows that around 50% of the biomarker information being published is related to oncology. "What will be interesting for us is examining the information trends for imaging biomarkers, is the distribution of use different? Having an information source that can show where major research is being focused can be valuable in allocating resources for a research organization," he says.

He expects neurology indications to grow rapidly, and new material covering many diseases is constantly being added.

The biomarker database is more than just a research tool, says Williams, it is also a competitive weapon. "If you're a biomarker expert you might want to look at what a competing organization is doing in imaging biomarkers. Are they looking to get into any new areas, where are they patenting? One of the strengths in the database is the variety of sources that we take information from. The patent, clinical trial and conference information is really valuable."

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The web-based database is made available through an annual subscription. Thomson Reuters has a custom solution team to install a mirror of the database on company systems, permitting companies to include their own data. And all the data is available in XML, "so clients can download the whole database by ftp and load it into their own systems if they wish," says Williams.

LOOKING AHEAD

Imaging biomarkers are the new kids on the block in drug development but their advantages, from saving time, detecting subtler drug effects and bolstering confidence in early results mean they look set to stay. In the clinic imaging biomarkers are providing earlier diagnosis and localization of disease, as well as helping clinicians navigate treatment by determining whether drugs are working — a strategy that will save money in the long term.

Challenges remain. Some imaging biomarkers need more evidence behind them before they can be relied upon as a true surrogate of clinical features; scientists are ankle-deep in data and processes must be standardized before imaging biomarkers can reach their full potential. But all these challenges are surmountable in the coming years as the research and medical communities work together and with regulatory agencies to make sure that imaging biomarkers have their full impact.

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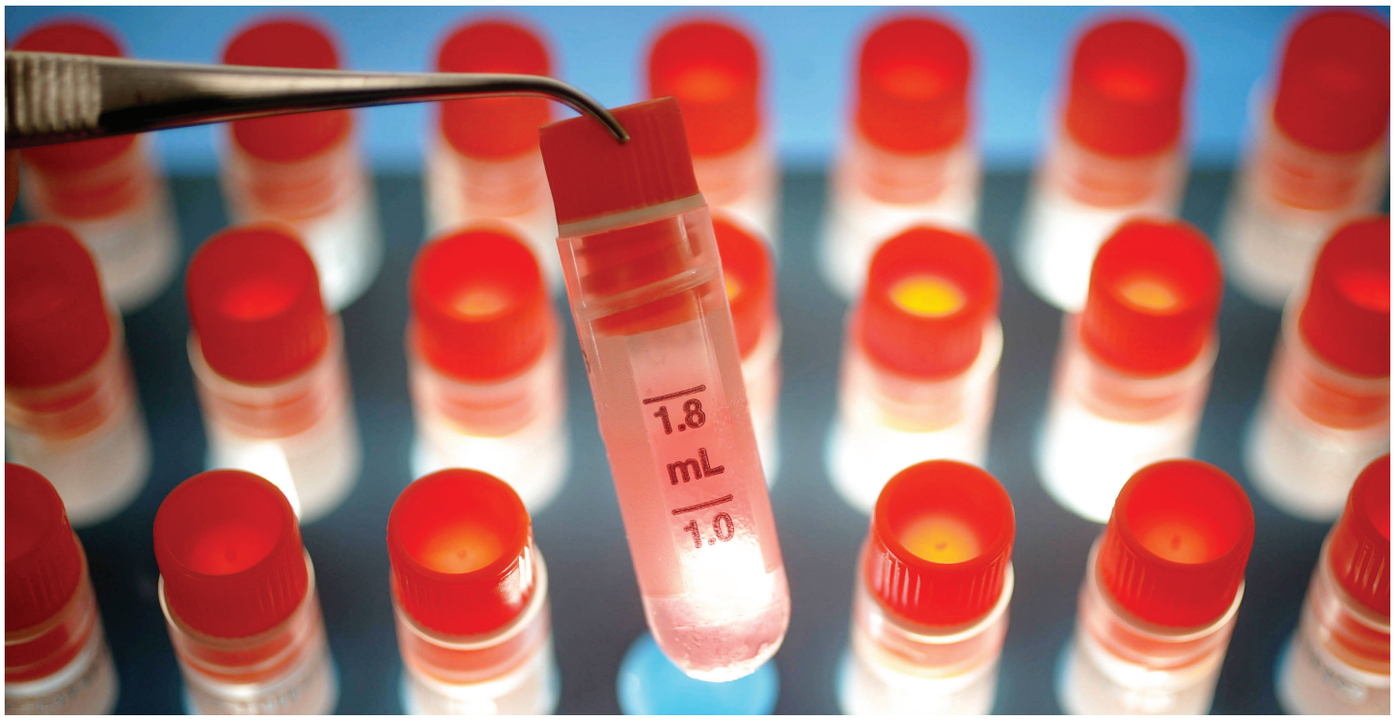

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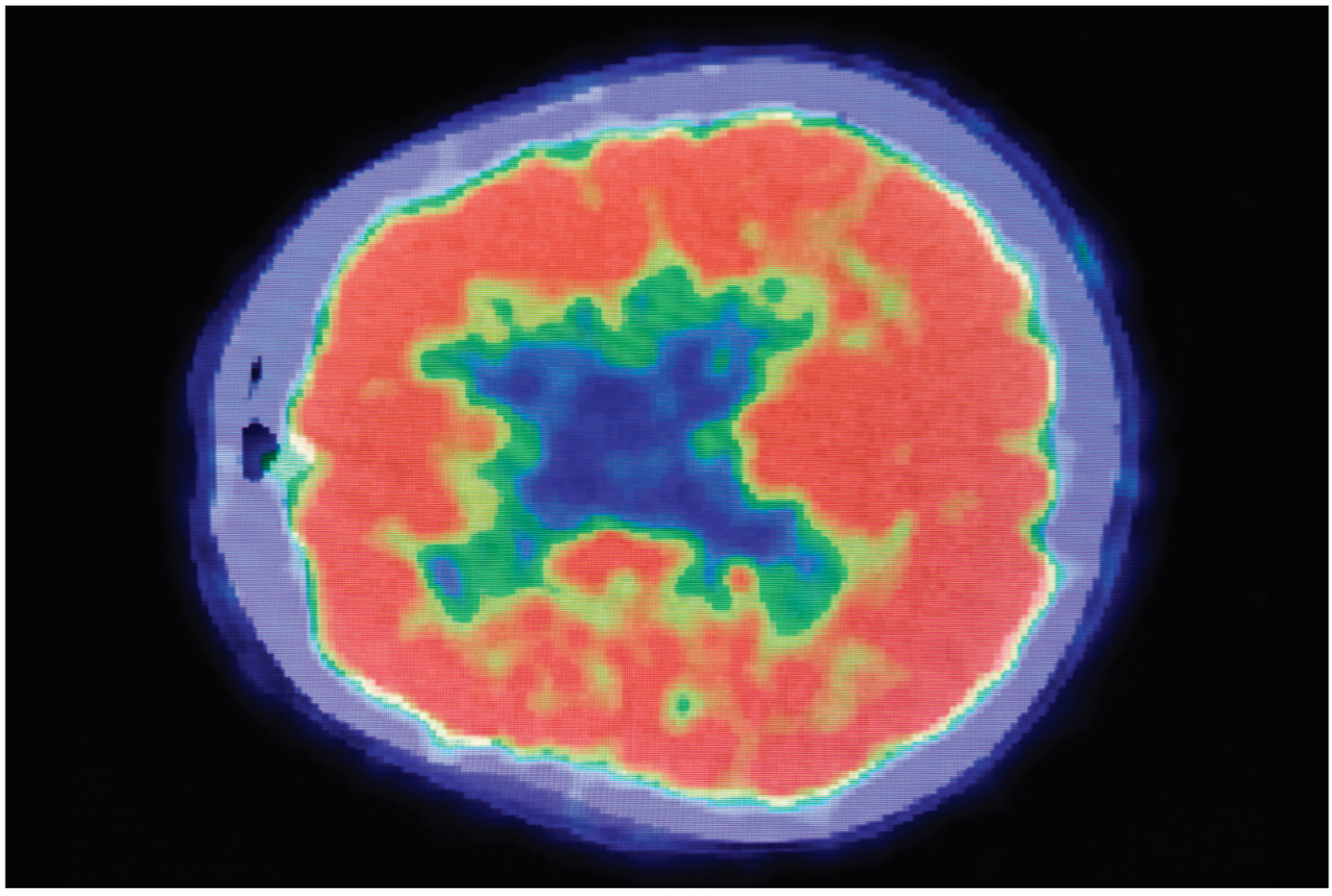

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