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Future Healthcare
It's all about functionality

Treatment of diseases has changed considerably in the past few decades, moving from a “one size fits all” perspective to what’s known as personalized medicine (“Personalized Medicine” or “PM”). Under PM, physicians use a patient’s individual genetic traits as the base upon which they create a tailored approach to identifying and treating disease.

We conclude with a brief discussion of the implications for medical equipment manufacturers and the role they can play in enhancing the results PM delivers.

The evolution of Personalized Medicine

Although first attempts to link an individual’s genetic characteristics with predisposition for a disease can be traced back to the early 20th century, the field of Personalized Medicine has gained significant importance in the past decade.1 Since the human genome project was finalized in 2003, the focus of medical research has undergone a paradigm shift from a “one size fits all” approach for all patients alike to a targeted, individualized treatment based on the patient’s genetic background.

A generally accepted definition of Personalized Medicine refers to all products and services that leverage the science of Omics-data to improve therapy decisions and provide the right treatment for the right person at the right time. This value proposition of PM is currently especially fulfilled by the fields of pharmacogenomics and in vitro diagnostics. Combining that with functional imaging capabilities results in a full set of patient information that can be used to describe the patient’s genotype (Omics-data and pharmacogenomics) as well as the phenotype (diagnostic imaging) at the same time.

Pharmacogenomics
Pharmacogenomics helps to evaluate targeted drugs for small patient populations, ideally resulting in higher efficacy (better response rates) and safety (reduced adverse reactions) based on the specific characteristics of individual patients’ genetic background.

In vitro diagnostics
In vitro diagnostics helps identify the genetic background of the patient to determine which drug treatment promises the best therapeutic results while minimizing adverse reactions.
Since the human genome project was finalized in 2003, the focus of medical research has undergone a paradigm shift from a “one size fits all” approach for all patients alike to a targeted, individualized treatment based on the patient’s genetic background.
How does imaging work in practice as a vital contributor to Personalized Medicine? We explore an example of its use in helping to detect, and identify the right treatment path for, colorectal cancer (CRC).
Diagnostic Imaging

Diagnostic Imaging comprises imaging devices and materials (e.g., tracers) used to visualize macrostructures such as organs and bones and microstructures such as cell types and molecular processes within cells. In clinical practice, diagnostic imaging is applied in all phases of personalized patient treatment and provides a number of advantages over diagnostic methods solely based on in vitro examinations. These advantages include:

- Ability to analyze anatomy, biochemical functions and metabolic processes over wide ranges of time and size scales
- Minimal or non-invasive data capturing without tissue destruction
- Provision of regional information with a functional or dynamic component (spatio-temporal localization)
- Possibility for real-time monitoring
- Support of minimally invasive therapy and reduced collateral effects through image-guided staging and therapy planning
- Cost-effective mass screening for high-risk groups with respect to certain cancer types such as breast or colon cancer

Four key imaging modalities

Four of the most important and best-known diagnostic imaging modalities are ultrasound, computed tomography (CT), magnetic resonance imaging (MRI) and nuclear medicine techniques such as positron emission tomography (PET) and single photon emission computed tomography (SPECT). These techniques differ in temporal and spatial resolution, field of view, sensitivity of the imaging system, and depth of biological process, as well as the availability of suitable tracer molecules.

Ultrasound

Diagnostic Ultrasonography, commonly known as Ultrasound, is a diagnostic imaging modality based on the echo characteristics of scattered sound waves. Due to its efficient processing, the Ultrasound modality can achieve high temporal resolution and thus display “live” images. To enable an excellent picture quality, Ultrasound can also use specialized contrast agents that possess high echogenicity (i.e., the ability to reflect waves). Although the Ultrasound method is highly developed, it is limited by the strong reflecting interaction of the waves with gas or hard tissue such as bones.

Magnetic resonance tomography (MRT)

The principle of magnetic resonance tomography is to detect electromagnetic radiation emitted by protons (water molecules of the body) during its spin relaxation within a strong external magnetic field. Besides the regular contrast visualization procedures where its strength is to visualize soft tissue, MRT modality can also be used to measure brain activity by detecting changes in blood flow. This functional MRT method is leveraged by the blood-oxygen-level-dependent (BOLD) contrast to map neural activities.

Computed Tomography (CT)

Computed tomography is an X-Ray-based medical imaging method that produces 2D and 3D cross-sectional images. Characteristics and dimensions of the internal structure can be visualized by computation of a series of X-Ray images. A three-dimensional view can be obtained by digital geometry processing in which the series of X-Ray pictures is taken around a single axis of rotation while either the probe or patient is moved along the axis. CT scanning can be enhanced by means of contrast agents.

PET and SPECT

PET and SPECT are nuclear medicine imaging techniques. The principle for these methods is the use of radioactive labeled tracer molecules and therefore the detection of gamma rays. A common tracer molecule for PET is fluorodeoxyglucose (F18-FDG), a positron emitter. These positrons are annihilated through interaction with surrounding electrons, which leads to gamma rays emission. SPECT uses a tracer that directly emits gamma radiation. Both PET and SPECT scans can be combined with CT or MRI scans to localize the radioactive hot spots in the body by overlaying the PET or SPECT scan with the 3D CT or MRI scan of the body.

Thus, depending on the characteristic requirements of the patient treatment phases, physicians must choose an appropriate imaging modality.

Imaging in action: characteristics, diagnosis and treatment of colorectal cancer

How does imaging work in practice as a vital contributor to Personalized Medicine? We explore an example of its use in helping to detect, and identify the right treatment path for, colorectal cancer (CRC).

In Germany and the United States, CRC is the second-most common cause of cancer death. Worldwide approximately 1.2 million new incidents of CRC will be detected in 2013, and the mortality rate is nearly 33 percent in the developed world. Currently, regular screening including occult blood testing and endoscopy, as well as radiology and further imaging modalities, enable a diagnosis at earlier stages. Due to improvements in detecting premalignant colorectal polyps through CRC screening, the mortality of CRC patients has declined in the past decade. However, there is still significant improvement required concerning time of diagnosis and adjuvant chemotherapy.

Imaging methods used during the treatment cycle of colorectal cancer

Digital imaging offers significant promise in helping physicians make greater inroads in the battle against CRC—from improving the screening, diagnosis and staging of CRC; to therapy planning, performance monitoring and post-treatment palliation.

Screening, diagnosis and staging of colorectal cancer

Screening for CRC is designed to detect advanced cancers or premalignant adenomas, from which at least 80 percent of CRC are believed to arise. Besides colonoscopy—an extremely accurate, but invasive, diagnostic test method due to its localization and biopsy abilities—CT colonography (virtual colonoscopy) provides additional radiographic diagnosis. CT colonography is an X-Ray based imaging method that uses low-dose radiation CT scanning to obtain an interior view of the colon.

CRC diagnosis is predominantly based on the results of colonoscopy or sigmoidoscopy combined with the...
results of the tumor biopsy. Next to physical examination, basic CT scans of the abdomen, chest and pelvis allow preoperative clinical staging, regional tumor extension and metastatic diseases identification. The sensitivity of CT for detection of malignant lymph nodes is higher for rectal than for colon cancers. However, CT scanning is not yet a reliable diagnostic method in the case of low-volume tumors. To accurately measure the spread of tumors to the surrounding tissues, MRI can also be used for diagnosis. Further MRI applications include global staging of the rectal tumor, guidance of the indication for radiation treatment, and metastases detection (predominantly in the liver).8

Once CRC is detected, staging can be conducted according to the Tumor, Metastases, Node classification process (TNM).9

Therapy planning, performance monitoring and post-treatment palliation

Pre-clinic studies show that serial FDG-PET examinations may aid treatment planning—in particular, for deciding the appropriate length of chemotherapy to maximize tumor response before surgical resection and to predict therapy effectiveness.10 Currently during therapy, physicians use CT, MRI and PET modalities on a recurring basis to provide information about the chronological development of tumor tissue and metastases. Therefore, consecutively taken pictures are being matched with each other, whereby in the best-case scenario the tumor volume decreases.

The post-treatment surveillance is conducted annually for the first three years primarily via computed tomography. Besides CT imaging, PET scanning can be adducted.

A tabular overview of the use of specific imaging modalities in CRC treatment phases is provided in Figure 1.

How Omics-data is used to characterize the type of CRC and what impact it has on the therapy

The premise of the human genome project was to use information about a patient’s complete genetic background to improve disease management, including diagnosis, staging and therapy. Additionally, the development of new molecular markers (biomarkers), which allows physicians to predict the individual response to therapy, represents a significant step toward individual treatment of patients.

For CRC, molecular and protein markers can already be extracted from blood- and stool-probes, as disturbed blood or lymph vessels, circulating tumor cells, and free-floating Deoxyribonucleic acid (DNA) and RNA end up in those probes.11 Diagnostic tests—such as advanced high-resolution melting assay (HRMA)—can identify aberrations and alterations. Mutations found in the DNA of CRC-positive probes are often within the gene KRAS, which encodes a protein that acts as a molecular switch. This switch turns on and off the propagation of growth factors. Mutated KRAS was first detected about 20 years ago in tumor-derived DNA in stool. Today, point mutations in KRAS can also be found in blood plasma of CRC patients.12

For KRAS, a clinical utility was established and, in addition to traditional laboratory assessment of the tumor, suggests benefits from anti-epidermal growth factor receptor (anti-EGFR) treatment, a therapy based on antibody usage.13 Unfortunately, no marker is yet suitable for population-wide screening, although some markers show better performance compared with current clinical Fecal occult blood Test (FOBT).14

DNA-based tests of blood and stool are still in progress, as sensitivity of markers needs to be optimized, and automated systems need to be developed to reduce costs and ensure reliability.15

In summary, imaging modalities are mainly used for tumor detection and characterization such as defining the tumor volume and shape. Nevertheless, the given imaging information is still an important contributor to determining the appropriate treatment path. Consequently, Omics-data also has to be considered as the alteration of certain genes indicates the usage of specific therapy methods, as shown with the KRAS example above. The “omics” aspect is where cancer treatment will be personalized in the future.

Imaging trends of the future: molecular imaging

In general, there are two ways to fight serious illnesses such as cancer. One way is the pharmacological aspect: developing better drugs used during therapy after cancer has been diagnosed and staged. The other, more efficient way is to diagnose cancer at an early stage, which consequently allows preventive actions that hinder further tumor growth. The science community currently aims to early-detect a cell mass of about 1 Mio cancer cells, which would lead to a size of about 1 square millimeter.

This section describes a possible approach to achieve early diagnosis by combining current state-of-the-art functional imaging trends with novel molecular tracers that only tag specific cancer cells. Hence, molecular imaging and the development of functional tracer molecules is becoming more and more important for early cancer detection and cancer specification.

Functional imaging: utilizing well-developed modalities for advanced visualization

The state of the art of common imaging modalities, such as CT or MRI, has progressed significantly in the past decades to an extent where resolution is no longer the most limiting factor. Instead, “abusing” those modalities for visualizing molecular processes or metabolisms, so-called functional imaging, is the prevailing trend. One well-established example, which is already clinically utilized for cancer staging and metastasis detection, is PET-CT, where the high-resolution CT image for anatomical localization is fused with the molecular-processes-visualizing PET scan.16

Another utilization in development is dynamic contrast enhanced (DCE) imaging, a repeated imaging technique that integrates excellent anatomic detail with assessment of vascular physiology.17 In general, acquired measures of DCE imaging include information about tumor blood flow and vascular permeability as well as interstitial pressure. This method can be applied to both CT and MRI modalities, of which the former, also known as Perfusion CT, is currently further developed due to the superior serial image acquisition of a
Figure 1: Overview of the use of imaging modalities in CRC treatment phases

<table>
<thead>
<tr>
<th>Screening &amp; Risk Assessment/Prognosis</th>
<th>Diagnosis &amp; Staging</th>
<th>Therapy planning &amp; performance monitoring</th>
<th>Post treatment and Palliation</th>
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<tr>
<td>CT colonography – expensive and might lead to biopsy</td>
<td>CT colonography for exact localization, surgical approaches</td>
<td>FDG PET for therapy planning</td>
<td>Surveillance: imaging (most commonly CT) once a year for the first 3 years PET to rule out recurrence</td>
</tr>
<tr>
<td>CT of the chest, abdomen, pelvis to identify metastases</td>
<td>CT of the chest, abdomen, pelvis to identify metastases</td>
<td>Repetition of CT, MRI, PET for comparison to survey tumor and metastases</td>
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<tr>
<td>High resolution MRI to accurately measure spread of tumor</td>
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<tr>
<td>FDG-PET to rule out occult extrahepatic spread that could change treatment strategy</td>
<td>FDG-PET for therapy planning</td>
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<tr>
<td>PET might eliminate the need for biopsy</td>
<td>Repetition of CT, MRI, PET for comparison to survey tumor and metastases</td>
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</table>

CRC
CT modality. However, the disadvantage lies in the radiation dose to which patients are exposed. With the improvement of MRI image acquisition, DCE MRI has also been developing, which is shown to be effective in detecting response to specific therapies.\cite{18}

As perfusion CT is becoming increasingly well established, DCE MRI only remains a promising method because of its lack of standardization across MR imaging analysis and acquisition has made study reproducibility a challenge.\cite{19}

Analogous to DCE imaging, which can be used for visualization of blood perfusion as mentioned above, the motion and perfusion probabilities of water molecules in the body can also be imaged. The technique of choice is called diffusion-weighted imaging (DWI). DWI is realized by applying diffusion-weighting gradients to MRI-imaging (DWI). DWI is applied for pre-clinical research.\cite{20} It has already been shown that certain fluorescent tracers can target tumor related antigens such as CD133, a surface-based cancer stem cell marker.\cite{21}

Thus, the research for further fluorescent agents—tagging specific cancer cell surface molecules in combination with efficient, high-quality imaging—seems promising.

Combining ‘macro’-imaging with ‘micro’-tracing to enable early cancer diagnosis

On the way to early cancer diagnosis, tracers that enable specific cell tagging would be the instrument of choice. Functional molecular imaging is a new and noninvasive strategy on a microscopic scale that can provide molecular and physiological information regarding cancer using various molecular-targeted imaging probes specific for cell surface biomarkers that are unique to cancer types.\cite{22} Hence, abnormal cells predisposed toward developing into cancer may be detected at an early stage, where the chance for curing patients is significantly higher.

CT imaging can provide anatomic and functional information with the appropriate X-Ray contrast agent, in this case gold nano-particles (AuNP). By attaching tumor-targeting molecules to the surface of AuNP, it may be possible to deliver these particles preferentially to tumor cells, similar to the uptake of FDG. AuNP has the advantages of being a non-radioactive tracer and it possesses significantly longer half-life than other X-Ray agents.\cite{23}

Of course, one could argue that CT scanning itself exposes patients to ionizing radiation without even considering potential radioactive contrast agents. The optical imaging method fluorescence molecular imaging (FMI) is an in vivo imaging method that utilizes fluorescent tracers—mostly ligands bound to proteins—which can be optically visualized. Due to scattering of light, the method is widely applied for pre-clinical research.\cite{24} It has already been shown that fluorescent tracers can target tumor related antigens such as CD133, a surface-based cancer stem cell marker.\cite{25}

One of the hot topics in oncology is the research on cancer stem cells (CSC), which may have tumor-initiating features that cause tumor growth, therapeutic failures and recurrence of the disease. Cell surface markers allow the isolation of CSCs for different kinds of cancer. Referring to the previous example on CRC, human colon cancer-initiating cells were identified in mice by tracing CD133.\cite{26}

Imaging on a molecular and functional level is one of the exciting new fields in medical imaging. Not far from now, gene and cell growth alterations will be non-invasively detectable and will serve as the basis of appropriate personalized therapies for the patient.

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**Figure 2: Components in the value proposition of Personalized Medicine**

*Diagnoses*

- Molecular imaging
  - Visualization of molecular processes in a patient’s body
  - Research of cellular networks and pathways of diseases

- In vitro diagnostics
  - Molecular fingerprint and genetic data about the patient
  - Identification of genetic properties such as gene mutations
  - Derivation of a patient’s genetic or proteomic state from biomarkers

*Therapy*

- Pharmacogenomics
  - Development of targeted drugs based on the specific characteristics of individual patients’ gene sequences
  - Higher efficacy (better response rates)
  - Improved safety (reduced adverse reactions)

*Personalized Patient Treatment*

- Screening risk assessment
- Diagnosis
- Staging therapy planning
- Therapy performance monitoring
- Palliation

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2. Derivation of a patient’s genetic or proteomic state from biomarkers

10. Development of targeted drugs based on the specific characteristics of individual patients’ gene sequences

15. Improved safety (reduced adverse reactions)
Implications for medical equipment manufacturers

Molecular imaging adds significant value to diagnostic methods based on *in vitro* examinations. Through the case study on colorectal cancer, we have shown how diagnostic imaging plays an important role in not only diagnosis, but also throughout all PM patient treatment phases.

A clear imaging trend can be identified toward functionality. While the resolution of medical images today seems sufficient for the day-to-day work in hospitals, functional imaging becomes increasingly important when dealing with more complex diseases such as cancer. Tagging specific types of cells will be the key discipline of the future in this scientific field.

In pre-clinical research, diagnostic imaging also plays an important role in the exploration of cellular networks and pathways of diseases, and helps determine which molecules are the most promising targets for potential drug treatment.

Figure 2 highlights the role of molecular imaging in relation to *in vitro* diagnostics and pharmacogenomics. While drug development is solely performed by pharmaceutical companies, medical equipment technology manufacturers and biotech companies provide the devices and materials for diagnostics throughout a personalized patient treatment.

The PM market is expected to grow to $42 billion annually by 2015 in the United States alone. Market research identifies PM as a strategic option for pharmaceutical companies to overcome what is called the “blockbuster dilemma” caused by expiring patents for drugs with high business volume and strong competition from the advent of generics drugs in previously highly profitable areas. Using PM principles, pharmaceutical companies differentiate through drugs with higher efficacy and safety. This leads to less competition in a highly segmented market and therefore higher pricing options to regain profitability.

The field of PM, therefore, provides significant market opportunities for medical equipment manufacturers. To tap these opportunities, medical equipment manufacturers should take a leading role in fostering collaboration among the various players participating in PM. Molecular imaging has the potential to provide detection of abnormal cells at a very early stage on the one hand and enhance our understanding of disease and drug activity during preclinical and clinical drug development on the other hand. This could help pharmaceutical companies determine which new-drug candidates seem most likely to be successful and halt the development of drugs that seem likely to ultimately fail.

Thus, the next generation of targeted imaging and therapeutic agents should be developed through close collaboration among medical equipment technology, biotechnology, and pharmaceutical companies.
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