

VIRTUAL GASTROINTESTINAL TRACT VIGOR++

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Technology Roadmap

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Executive Summary

This roadmap is a deliverable of the VIGOR++, a gastrointestinal (GI) tract focused project in the overall set of projects making up the Virtual Physiological Human (VPH) programme. Its purpose is to inform scientists, clinicians, system integrators and other stakeholders of likely developments and where the contributions of various parties fit in helping to realise the overall vision.

VPH is a collective framework that aims to build integrated computer models of the mechanical, physical and biochemical functions of the human body at various different scales using a range of patient data, anatomical, physiological and pathological, along with predictive simulations. These are intended to enable a major shift in healthcare approach that will improve efficiency and effectiveness with a patient-centric and preventative strategy.

VIGOR++ is focussed on a VPH model for improved detection and assessment of Crohn's disease. It takes MRI, endoscopy and histopathological input data from historical records and dedicated medical studies and uses advances in image analysis, modelling and interactive visualisation to build the model.

The roadmap describes a future beyond the focus of VIGOR++ but building upon its achievements. Its scope extends to a model that describes other GI diseases and some degree of interaction between this model and other related organ models. The roadmap was built through consultation with various experts and stakeholders including clinicians, scientists and engineers, patient support groups and others. There was also extensive review of published information.

Two forms of the roadmap are presented – a descriptive version and a diagrammatic version that gives a summary view but makes clearer how the various aspects or layers relate to each other. The roadmap timeline is from 2012 to 2022.

The vision for 2022 is a healthcare scenario where a patient has a personalised virtual GI tract model that can be periodically updated with new MRI scan data thus avoiding the need for frequent uncomfortable invasive investigation and allowing better disease management. For a newer generation of patients with known genetic predisposition to GI diseases there is the opportunity for earlier and easier monitoring and therefore effective disease prevention. Because the tools are based on model and imaging data they lend themselves to remote healthcare or at least a shift away from a hospital-centred approach.

A number of drivers that will affect the likelihood of this vision being realised are explored. Business or market drivers include the increasing demands and expectations placed on national healthcare systems by the need to deal with an expanding and ageing population with increased chronic health conditions. GI diseases in particular are increasingly recognised as a major problem in the developed world. Product or service drivers include a growing demand from clinicians for improved tools for better detection, diagnosis and visualisation of GI conditions. Trends towards ICT enabled healthcare, cloud computing and the need for more objective and quantitative assessments will also support this model-based approach. Technology drivers include advances anticipated in MRI image quality, image sequence protocols, image processing techniques, image registration and segmentation, machine learning applied to modelling and classification tasks, interactive visualisation through combining images and other inputs in multiscale representation, compressive imaging and cloud computing.

The expectations of business and the market set a number of targets for the roadmap over the 10 year period. Integrated digitised medical records will become the norm across major healthcare systems by 2014/15. Large-scale screening programmes for high-risk people should be being carried out by 2022. Routine Crohn's disease diagnosis using the VIGOR++ model should be in place by 2016 followed by the model being integrated with other related organ models by 2022. The cost and time of diagnosis will be reduced from approx. €1k / 5hrs now to

€300 / 1hr by 2016. Small scale systems deployment (20 users) will be achieved by the end of the VIGOR++ project (2014) and large scale deployment (600 users) by 2018. There will be an increased involvement of well-informed patients (so called Super Patients) in their own healthcare choices facilitated by ICT-based solutions.

In order to address the market or business needs described above a number of products, processes or services are expected. Workflows will be developed to accommodate large-scale screening and to enable the 'Super Patient' to manage their own health. Remote and offline examination will become an option and will evolve to remote real-time diagnosis. Automation at various stages of the protocol will enable increased speed of diagnosis. Integrated VPH models, linking Crohn's / GI disease models to cancer of the bowel will be developed and these will then be extended to other cancers. The model tool will also be used for '*in silico*' drug discovery before 2022. New finance models will be developed to pay for the new approach to healthcare with a range of service models including recognition of the opportunity to target several potential customer types.

To deliver the products and services that address the market and business needs there will have to be technological advances in several areas, particularly in image analysis, modelling and classification and interactive visualisation.

In image analysis scan speed will improve to around 10 minutes for a full abdominal scan by 2022. MRI resolution will improve to around 1-2 mm by 2022. Image quality and utility will be improved by changes to sequence design. Significant further work is needed in the area of selecting and combining features and in addressing registration problems. Image processing will be improved by energy minimisation tools and correlation to *a priori* information. Optimised algorithms will enable near real-time image segmentation and registration. Multiscale image correlation will continue to be a major challenge that will not be fully addressed by 2022. DICOM will continue to be the dominant format.

For modelling and classification supervised learning will be most suited to developing the GI model. Expert user involvement to identify regions to be classified and expert feedback to improve classifiers will continue for the foreseeable future. Further work will be needed on measuring the most representative features among several possible ones such as wall thickness, textures, shapes, signal intensity or edge features. Classification speed will not be an issue for run time (training is what takes time) until genomic feature sets become incorporated. On-going research will determine the optimal size/structure of superpixels/voxels which are useful for feature extraction, capture redundancy, and reducing complexity of processing tasks. Statistical features coupled with segmentation information will help calculate the CDEIS score and compare evolution of disease amongst patients.

For visualisation significant research will be needed to address image fusion at different scales e.g. when using different medical imaging modalities. There will be combined interactive visualisations where you can move a cursor over a 3D volume to call up further clinical information – probably the CDEIS scores. New techniques will emerge to deal with the representation from huge multi-dimensional data sets e.g. the trend to compressed imaging or similar will impact in the visualisation field. Mobile device use will be enabled by generating the visualisations at data centres thus only needing to transmit the final image. Augmented- and mixed-reality methods are still in their infancy but are likely to be used in niche applications including training of new physicians and radiologists.

Advances in the area of capsule endoscopy are also explored as these have the potential to provide complementary input data to models and potentially to provide alternative approaches to diagnosis in some cases. The main anticipated improvements to this technique are in extending the measurement capabilities from simple visible imaging, adding the ability to control capsule movement, the potential for smart targeted drug delivery from the capsule and in the

long term the possibility to take biopsy samples and even carry out more complicated micro-surgical procedures using the capsule as a platform.

Other areas identified for advancement include training of clinicians in the use of the tools and the inclusion of such ICT-based tools in academic curricula to prepare a new generation of healthcare professionals for the future.

Business model development will also require attention in order to both deal with the cost of implementing the new approach to healthcare and also to ensure that the maximum benefit is extracted from the opportunity it presents. Whilst it is generally considered too early yet to specify the model most likely to be sustainable, there is a clear need to work on understanding what benefits all potential stakeholders could gain from the information in this ICT enabled healthcare toolset and what value they would put on such information. These models will likely need to consider a more patient centric approach with associated issues of data ownership, privacy, consent and assurances on use. There may also be mixed business models that involve a trusted intermediary or broker hosting a service and multiple revenue streams to match the needs and resources of several very different stakeholders such as healthcare providers, governments, insurance companies, pharmaceutical companies and patients.

Finally, social media is already an important tool in providing patients with discrete information and advice on living with GI diseases. These approaches are also likely to help with growing awareness of the alternatives provided by the VPH approach to GI healthcare. They may even play a role in driving the patient centric approach forward more quickly.

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1 Introduction

This roadmap is one of the deliverables of the VIGOR++ project, a gastrointestinal tract focused project in the overall set of projects making up the Virtual Physiological Human programme.

1.1 The Virtual Physiological Human

The Virtual Physiological Human (VPH)¹ is a methodological and technological framework that aims to enable collaborative investigation of the human body as a single complex system. The collective framework will make it possible to share resources and observations formed by institutions and organisations creating disparate, but integrated computer models of the mechanical, physical and biochemical functions of a living human body.

The VPH is a framework which aims to be descriptive, integrative and predictive:

Descriptive. The framework should allow observations made in laboratories, hospitals and the field, at a variety of locations situated anywhere in the world, to be collected, catalogued, organised, shared and combined in any possible way.

Integrative. The framework should enable experts to analyse these observations collaboratively and develop systemic hypotheses that involve the knowledge of multiple scientific disciplines.

Predictive. The framework should make it possible to interconnect predictive models defined at different scales, with multiple methods and varying levels of detail, into systemic networks that solidify those systemic hypotheses; it should also make it possible to verify their validity by comparison with other clinical or laboratory observations.

The framework is formed by large collections of anatomical, physiological, and pathological data stored in digital format, by predictive simulations developed from these collections, and by services intended to support researchers in the creation and maintenance of these models, as well as in the creation of end-user technologies to be used in the clinical practice. VPH models aim to integrate physiological processes across different length and time scales (multi-scale modelling). These models make possible the combination of patient-specific data with population-based representations. The objective is to develop a systemic approach which avoids a reductionist approach and seeks not to subdivide biological systems in any particular way by dimensional scale (body, organ, tissue, cells, molecules), by scientific discipline (biology, physiology, biophysics biochemistry, molecular biology, bioengineering) or anatomical sub-system (cardiovascular, musculoskeletal, gastrointestinal, etc.).

1.1.1 The VIGOR++ project

VIGOR++² is working to improve detection and accurate assessment of Crohn's disease, an autoimmune gastrointestinal condition with 700,000 diagnosed cases across Europe. By combining advances in image analysis, modelling and interactive visualisation VIGOR++ will create a personalised model of the gastrointestinal tract reducing the need for frequent and often invasive examinations.

The consortium comprises seven partners, from four European countries, with the following responsibilities:

- TU Delft: Image analysis and project coordination

¹http://en.wikipedia.org/wiki/Virtual_Physiological_Human

²more information on VIGOR++ can be found at <http://www.vigorpp.eu>

- University College London Hospitals: Clinical Data Acquisition and Data Management
- ETH Zürich: Modelling and classification
- Zuse Institute Berlin: Interactive Visualisation
- Biotronics3D Ltd: System Architecture and Integration
- Academic Medical Centre, University of Amsterdam: Clinical Application and Validation
- Vodera Ltd: Dissemination, Exploitation and New Applications

1.1.1.1 The motivation

Crohn's disease is a chronic condition of the gastrointestinal (GI) tract. Colonoscopy in combination with the assessment of biopsy samples is considered the reference standard for diagnosis. However, the procedure is invasive and requires extensive bowel preparation which is poorly tolerated by most patients. Also, the technique primarily gives information on superficial abnormalities (limited to direct visual inspection of the bowel lining or tissue samples from the inner bowel layers only), without much information on the intestinal wall or extra-intestinal disease, both of which are very important in Crohn's disease. As a consequence, radiological imaging techniques have become important additional tools for non-invasively evaluating disease activity in Crohn's disease and by providing information about the bowel lumen, bowel wall and extra enteric soft tissues.

Crohn's is also characterised by alternating periods of increased and reduced disease activity. It is therefore important to regularly assess the severity of the disease in order to adjust the treatment accordingly. At the moment, therefore, frequent and often invasive examinations are an on-going experience for sufferers. According to a recent survey conducted by EFCCA across Europe, 74% of patients have taken time off work in the last year due to IBD – 26% for over 25 days. Disease severity and ability to work seem to correlate. 61% feel stressed about taking time off, 25% have received complaints or unfair comments, and 21% have suffered discrimination. VIGOR++ aims to change this.

1.1.1.2 The approach

The VIGOR++ approach will take as input laboratory, MRI, colonoscopy and microscopy (histopathology) data from both historical records and dedicated trials in order to develop a personalised GI tract model.

Feature selection from the clinical data will be employed to predict features from the molecular to cellular scale (microscopy/colonoscopy) and from descriptive properties at the organ to patient scales (MRI/laboratory). MRI images are central to the analysis as they allow the measurement of the thickness of the intestinal wall, the degree of vascularisation and help distinguish the various layers of the intestine.

Part of the development comprises the creation of a normal representation of the GI tract, as well as ICT tools to detect and rate deviations from normality on an index of disease severity. Importantly, whilst the colonoscopy and the histopathology data will enable the development of accurate prediction models, the ultimate goal is to be able to predict the disease state based on non-invasive imaging.

In VIGOR++ several levels of classification are being considered, namely voxel-wise classification, segment-wise classification and bowel-wise / patient-wise classification (see D6.2 System Architecture Report).

So in the future, the VIGOR++ tools will mean that a simple, non-invasive, low risk MRI scan used in conjunction with the personalised model will be sufficient to diagnose the disease and monitor its severity. This will improve the lives of Crohn's disease sufferers enormously.

1.1.1.3 Building the tools

VIGOR++ will combine proven image analysis techniques to identify regions of interest and register the MR images to compensate for patient movement. In addition, descriptive properties of Crohn's disease activity will be measured in the MR, endoscopic and histopathological images. The features obtained will be the basis of the modelling and classification tasks.

Pattern recognition techniques will be applied to detect and rate abnormalities, so that a combined and quantitative, clinical disease severity index can be accurately established.

A visualisation software toolbox will be designed to enable interactive visualisation of GI wall tissue properties. It will feature techniques for concurrent visualisation of the multiscale clinical patient data as well as the properties measured by image analysis and classification.

The system will be tested throughout the project to ensure both accuracy and usability in a clinical setting. To ensure validation, the clinical benefit will be demonstrated in a study in which the tools' ability to predict Crohn's disease is assessed. A preliminary study will also be performed in which the effect of therapy will be demonstrated.

1.1.1.4 The benefits

The patients will benefit from the VIGOR++ tools through disease management that is less disruptive to their day-to-day lives and which will also empower them via web portals to play an active role in their care. This has important financial benefits as the disease is generally most prevalent during the patients' most economically active years.

Clinicians will benefit from increased efficiency of diagnosis and integration with treatment planning, in particular the ability to assess disease progress and predict potential complications. The minimisation of the need for optical colonoscopy particularly for patients unable to tolerate bowel preparation will be welcomed. The tools will also help support shared decision making with patients.

National health systems and private healthcare insurers will benefit from reduced diagnosis and disease management cost through higher throughput and reduced hospital stays. They will also have improved return on investment for technology such as MRI scanners.

The tools should also help pharmaceutical companies carry out more efficient and less costly clinical trials by providing accurate, quantitative descriptors of therapy effect.

1.2 Background and Objectives of the Report

A technology or product roadmap is a layered, structured and connected view of the future development of business or market needs, the products or services that address them and the technologies that allow the products or services to be delivered.

Such roadmaps are primarily a communication tool. They conveniently bring together the information at these various levels and present it in such a way as to be useful to multiple stakeholders. They help with the identification of gaps in technology provision, help indicate where investment of effort and funding is needed and help various stakeholders to understand where their contribution fits with that of others in helping to realise the overall vision.

The core of a roadmap is a vision of the future and the mapping out over time of the changes to the current state of play to achieve this vision.

A roadmap for the Virtual Gastrointestinal Tract is presented here as one of the deliverables of the VIGOR++ project. It serves to take the technology developed within the project focused on Crohn's disease and place it in context of the wider challenge of developing a virtual model of the GI tract.

1.2.1 Audiences

This roadmap has a number of potential audiences. It is anticipated that it may be useful to:

- The project consortium – to help the various partners understand where their technology fits with that of other partners and what particular developments are required for both the project and the overall roadmap vision to come together
- Other VPH related researchers – to show the potential developments in the virtual GI tract area as well as to make visible the opportunities for those working on related technologies to contribute to the development
- Funding bodies e.g. EC – to illustrate the areas of technology that require funding either now or in the future in order that the vision be realised
- The industry supply chain – to enable them to plan for engagement with the technologies and the demonstrators to be developed so as to be well positioned to deliver the products and services of the future
- Clinical Research Firms – to help them compare the various previous, the current technologies, and the technologies which will replace these
- Patient representatives and the wider public – to help communicate the possibilities for future diagnosis and treatment and also to provide the opportunity for them to raise any concerns or refinements to requirements
- Business research and consulting service providers – to help correlate technical advances with shifts in healthcare provision

1.2.2 Approach

The roadmap was built through a series of exercises involving a range of experts and stakeholders. The vision was defined by members of the VIGOR++ project and describes a scope beyond that of the project in both timeframe and outcomes.

The timeline for the roadmap was set at 10 years i.e. 2012 – 2022. This was considered sufficiently long for major changes but short enough to make predictions sensible.

Information was gathered from a variety of sources:

- Research publications, journals, magazines, newspapers, industry reports, other roadmaps, strategy documents, conferences, research papers (see Appendix A for references)
- Discussions with clinicians
- Discussions with scientists and engineers involved in the technology fields required
- Discussions with patient support groups

In examining each of these sources the general approach was to understand what is wanted for the future, what is expected to happen anyway, what further is needed and what is actually considered possible.

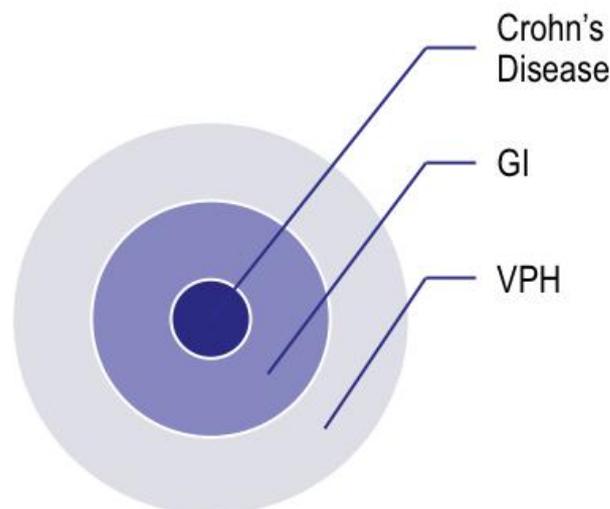
The main elements of the roadmapping process were:

- Developing and describing a vision of the future
- Understanding the drivers and constraints that are affecting the likely realisation of this vision
- Understanding the business and market needs
- Describing the likely products and services that will be developed and evolve in order to address the needs
- Describing the various strands of technology development that need to happen in order to deliver the products and services

- Understanding the other resources required e.g. training, standards, funds, skills etc.
- Following the construction of the roadmap, its content was validated by discussion with relevant experts in the fields.

1.2.3 Scope

The roadmap describes a future beyond the focus of the VIGOR++ project which is limited to describing a model for Crohn's Disease. The focus is on structural and functional conditions of the bowel, where the former represent readily identifiable organic disorders (e.g. colorectal cancer, UC, Crohn's disease, diverticular disease), and the latter, those where symptoms are unexplained by conventional investigations (e.g. irritable bowel syndrome, chronic constipation). Thus, it extends this work to cover all diseases of the GI tract and some degree of interaction between this model and other related organ models. The scope is described diagrammatically in the figure below. With the time frame of 10 years from 2012 and the complexity of the tasks it does not extend to describing a roadmap for the full Virtual Physiological Human. This task is longer term, more speculative and is the subject of efforts by a wider group through the VPH FET project: Advanced Technologies for the Future of the Virtual Physiological Human.



Several of the topics covered by the roadmapping exercise interact with broad disciplines such as: medical physics/engineering; biological science (biochemistry, microbiology, physiology and genetics); clinical services and public health policy.

1.2.4 How to read the roadmap

The roadmap is presented in two forms – a diagram or graphical version and a descriptive version. The graphical version is a summary form that makes clear how the challenge of describing the evolution to the vision is achieved i.e. by breaking it down into a number of interrelated layers. The descriptive version is useful for understanding the content in more detail.

The easiest approach to reading the roadmap is to start with the vision statement (next section) and then read the graphical version from top to bottom. Essentially, after consideration of the drivers and constraints one should examine the business and market needs of the future. These are what define the 'why' question of the roadmap. Why are we doing it, why is it needed, why invest, why plan around this future?

Next one should read the product and services layer. This relates to 'what' is needed to address the needs already described. What are the products or services or evolutions of them that will be required at each step into the future in order to realise the vision.

Then one should look at the technology layer. This is the 'how' layer. It describes a number of different technology strands. The development of each of these technologies at the right time is required in order to be able to deliver those required products or services. Some of these technologies will develop in the required way due to other applications / needs while some will need encouraging specifically for the development of the product or service mentioned.

Finally, there is an 'other resources' layer which underpins the layers above. This layer describes a range of things that are necessary in order for everything to come together to deliver on the vision. This can include the development of skills and training, the securing of funds, the development and acceptance of standardised approaches etc.

1.2.5 Comments and Feedback

Roadmaps are built on several assumptions and many of the market forces and R&D trends evolve over time in ways that were not necessarily predicted. This roadmap is therefore intended to be 'living document', open to the community discussion. Earlier versions of this document have been presented at the VIGOR++ Annual Workshop held in London on 7 Feb 2012 (vigorpp.eu/workshop2012) as well as project internal meetings. Feedback for future versions is encouraged. To do so please email: roadmap@vigorpp.eu

2 Roadmap 2012-2022

2.1 Vision 2022

The development of the roadmap is built upon a vision for the future. With a ten year time frame this vision for 2022 is described below:

2.1.1 A vision of gastrointestinal tract healthcare in 2022

Jane and her son Noel attend a clinic at their local body-scanning centre. Whilst not at a hospital, this centre has a range of non-invasive scanning technologies at its disposal. It is also able to remotely access expert clinical interpretation and automated analysis.

Jane is a long term sufferer of Crohn's disease. She was diagnosed when she was in her 30's after being hospitalised, suffering from severe symptoms. After a recent flare up she has come in to have her treatment altered to manage the condition better. She has accepted that for her the best hope is a lifetime of careful management of the condition so avoiding surgery.

This is now possible without the discomfort and inconvenience of repeated invasive diagnosis. The key to this is her personalised virtual gastrointestinal (GI) tract³ model and an updated MRI scan; a quick and painless way for the doctors to keep close track of the development of her condition and alter treatment accordingly.

In the clinic the technician takes a new MRI scan and uploads it to her personalised GI model stored remotely on the 'Cloud'. Using the automatic analysis tools the cause of the flare up in symptoms is identified and her medication is altered. Had there been any unusual findings a doctor could have been consulted remotely.

This is a far cry from the early days of the disease where she used to have a colonoscopy and treatment based on only partial information. The disease never seemed to be under control. But really, while she is happy that disease management has just become a way of life and is reasonably easy, Jane wishes that she had been diagnosed a lot earlier.

Noel has come along too as his genome suggests a predisposition to GI diseases. He is part of the lucky generation. This is Noel's first clinic appointment. He will receive an MRI scan and the latest image analysis techniques and visualisation tools enable the building of a personalised model of his GI tract non-invasively and long before he exhibits any symptoms of any GI problems.

He will periodically have his scan updated and his GI tract carefully monitored. At the first signs of disease preventative action can be taken but also clear advice on diet and lifestyle are able to give him the best chance of preventing the development of the disease. By using these techniques early on the young people of today far fewer should ever develop acute symptoms and the costs to healthcare systems will therefore be much lower.

In summary, the vision is one of a future with a personalised virtual gastrointestinal (GI) tract model that can be updated with just an MRI scan. Being sufficiently good without the need for colonoscopy gives a quick and painless way to keep close track of the development of a patient's condition and alter treatment accordingly. Already established sufferers get better disease management. The next generation of patients with genetic predisposition to GI diseases get early monitoring and preventative action e.g. lifestyle and diet. This level of patient convenience is enabled through local clinics with remote access to clinicians as necessary.

³Also called digestive tract or alimentary canal) is the system of organs that takes in food, digests it to extract energy and nutrients, and expels the remaining waste.

2.2 Drivers of success

A number of factors are driving or constraining the realisation of the vision described above. These may be drivers of the market, the products or services or even of the technology developments.

2.2.1 Business or market drivers

The business or market is driven by a range of trends. At the political level there are increasing demands and expectations placed on national health systems at a time when public budgets are under severe strain. The population is ageing and with this has come the need to deal with an expanding array of chronic health conditions over longer lifetimes. In many societies it is expected that the government will fund such provision. In redesigning national health systems and in insurance-led systems there is therefore an increasing trend to payment by results or health outcomes and this is leading to pressure to adopt more effective treatments. There is also a recognition that modern medicine mainly concentrates on clinical signs and less on prevention. More advanced tools that combine and analyse the heterogeneous data collected in clinical practice should allow better understanding of the systemic effects of diseases and pathology. Only then can truly predictive tools and preventive health politics be developed. Such an approach should also allow clinicians to develop more cost-effective alternative therapies and reduce health-related social costs. Efforts to implement change though are somewhat inhibited by increasingly complex regulatory approvals processes. At present adoption rates of new medical technology is driven almost entirely by reimbursement codes that depend upon politics and legislation associated with the prevalence of certain diseases/conditions and the need to reduce healthcare costs for the overall healthcare system. There are, however, also efforts to develop standards that enable integration of approaches and acceptance of VPH/ICT-based approaches to healthcare.

At the economic level the business or market is driven by various cost reduction strategies. There is a need to achieve a more efficient and effective healthcare system to cope with ageing population and rising healthcare costs. New business models are being developed to allow this. Efficiency and effectiveness are expected to be supported by a paradigm shift from the traditional hospital-centred and reactive healthcare delivery model toward a person-centred and preventive one. It is also anticipated that the trend to digitised medical records will continue to enable more efficient diagnosis and treatment. By developing a more connected healthcare system it will also be more feasible for healthcare to move into the community and away from acute health trusts – particularly for management of chronic but non-emergency conditions. The rise of the informed patient is also developing a consumer market driving a trend to cheap, disposable healthcare devices. It is also expected that the tools will be very valuable to, for instance, pharmaceutical companies since clinical trials can be much more efficient by having accurate, quantitative descriptors of therapy effect and so reduce the high cost. There is even the potential promise of individualised clinical trials which would have the added economic benefit of better targeting of drugs to those where they are likely to be effective.

The primary social driver of this business or market is the growing recognition of the extent of GI diseases which are a huge healthcare problem in the Western World, affecting millions of people. It is increasingly recognised that there is a need for early diagnosis, improved treatment, reduced clinical risks associated with interventions and eventually, hopefully, and prevention of the disease. There is also a trend towards the more empowered patient. With greater availability of health information, the internet is the first port of call for many people. The patient of the future will own and manage their personal health record and be able to provide digital health records to the service provider of their choice. There is a growing acceptance of

ICT-based tools and e-Health infrastructures throughout European healthcare and this will drive acceptance of modelling-based solutions and the VPH concept in general. The general desire for less animal experimentation and drugs testing should also support the move to VPH type tools.

2.2.2 Product, service or processes drivers

To date there has been excessive fragmentation and over-specialisation of expertise in healthcare resulting in something of a silo approach to the diagnosis and treatment of conditions. This results in duplication of effort, a lack of integrated information management and often sub-optimal treatment where co-morbidity of chronic conditions are not treated holistically. The constraints of this approach are being countered now by a range of drivers.

Physicians are more frequently demanding advanced tools to improve the detection and visualisation of abnormalities, to enhance the communication between fellow doctors, and to quantitatively assess the outcome of interventions. This trend is likely to be further supported by future approaches that increasingly integrate observations with models to enable better and easier prediction. Personalisation trends will be supported by moves to bioprofiling of individuals to determine their predisposition to various diseases. The evolving trend towards personalised healthcare will drive the need for products and services based around ownership of your own electronic healthcare record. This will be facilitated by the creation of more computer model-based records which are able to take various digital inputs and be easily updated. In the area of GI tract disease there is likely to be a trend to more objective, reproducible and quantifiable activity scoring compared to the present indices. These activity indices will, in most cases, be derived by non-invasive examination.

The trend towards ICT-based products and services will be further enabled by on-going development of cloud computing solutions. This will allow online storage and processing of data and will facilitate the remote delivery of healthcare. Digital medical information systems that are reliable and scalable will open up new possibilities in automated diagnosis and treatment. A new generation of integrated tools underpinning easy to use, standardised and well maintained applications for the modelling of the GI tract will play a key role in realising the roadmap's vision. A discussion of the drivers behind those tools follows.

2.2.3 Technology drivers

Technology drivers in a number of fields will come together to enable the delivery of the healthcare vision described earlier. Many of these advances in technology will be driven by the needs of other sectors or fields but the benefits will also be gained in the areas relating to delivering this personalised GI tract model.

In this section we cover some of the top level technology drivers that will influence the direction in which the underpinning technologies will evolve. The detail of the required technical advances required in order to realise the vision of this roadmap are described in a section 4.5.

In the area of image analysis improvements will be driven to some extent by increased resolution of MRI and probably more so by the delivery of more useful images through development of new imaging sequence protocols. Molecular imaging is another potential development. It enables the visualisation of the cellular function and the follow-up of the molecular process in living organisms without disturbing them. Biomarkers are used to interact chemically with their surroundings and in turn alter the image according to molecular changes occurring within the area of interest. VIGOR++ partner AMC are working on molecular imaging with MRI for targeted bowel imaging but this will take at least 5 years before it reaches the clinical arena.

Developments in the field of compressive sensing/imaging are likely to help. Further improvements in energy minimisation techniques are likely to impact image processing. Advances will also be made in image registration and segmentation and this should help any moves to delivering a multi-scale imaging product.

Modelling and classification is likely to be driven by improvements in feature selection techniques and in machine learning algorithms, particularly in the area of supervised learning. Concepts such as cloud-based solutions will require exploitation of improved remote computing power.

Interactive visualisation will underpin better diagnosis. It will be driven by improved techniques for combining images and other information and by better rendering techniques. Improvements in computing power and capabilities to use compressed sensing/imaging will assist in dealing with such large data sets. Display of visualisations will be supported by developments in large, high resolution displays in some applications but also by the proliferation of tablet computers and other mobile displays although this will require different strategies with the rendering power hosted remotely from the display device. This trend will inevitably be driven by moves to cloud and grid computing.

Other technology developments may drive alternative solutions. There is the possibility that swallowable 'pill cameras' and other diagnostic microsystems may provide an alternative view of the GI tract. This may either compete directly with the MRI approach in the very long run if options to image through the bowel wall are introduced or more likely in the medium term actually complement the approach currently being developed. At present new imaging modalities do not appear to be likely to supplant MRI in the next 10 years but there is much work in the medical imaging field and breakthroughs in other techniques cannot be ruled out. To compete, these would need to address issues of improved cross-sectional imaging, patient comfort, cost and the use of non-ionising radiation.

Much of the above and the delivery of ICT-based solutions more generally is to be driven by improvements in computing power, driven by Moore's Law, and by improved strategies for managing the use of computing power e.g. remote processing and storage and mobile display. In addition, advances in the area of wireless data transmission and associated standards will help in enabling the use of mobile devices in the healthcare environment.

2.2.4 Other drivers

ICT-based education and training for future doctors and medical researchers as well as an increased focus on ICT-based healthcare in academic curricula will help. On-going investment in the ICT or e-health infrastructure will facilitate the uptake of VPH related approaches. The formation of a VPH Institute will sustain the coordination of all academic, governmental, industrial and societal stakeholders' efforts towards the common goal of developing an integrative biomedical science and technology that makes the VPH vision practically possible. Further R&D investment in VPH will drive both capabilities and the acceptance of the approach. The emergence of commercial suppliers will come as the likelihood of acceptance by healthcare systems grows. This will be driven by the demonstration of successes in the wider family of VPH projects and growing awareness of the potential of the technology. This awareness is likely to come through the dissemination efforts of the many different projects, the efforts of the VPH Network of Excellence and through growing reference in social media. The insurance companies are likely to drive uptake through their control and funding of private healthcare. Their focus on healthcare as a business is likely to make them more responsive to adopting new more efficient and effective approaches than national public health systems. Regulation of new medical technology may affect the rate of developments. There is a significant variation in the

risk adversity among national regulators⁴ and the complex systems of financing health care are also a problem.

2.3 Business & market

The expectations of business and the market set a number of targets for the roadmap over the next 10 years. The cost and speed of diagnosis for Crohn's disease will come down significantly. At present it is an entirely manual process and takes around 5 hours for diagnosis and costs around €1,000. By around 2013 it is likely that a semi-automated evaluation process will already be being tried out and this should start to bring down time and costs. By 2016 it is expected that driven by greater automation this will be reduced to a diagnosis time of 1 hour and a cost of around €300. At this point diagnosis of Crohn's disease using the VIGOR++ tools will be routine although not yet widely rolled out. By 2014-2015 it is expected that there will be small-scale deployment of the VIGOR++ tool kit, with around 20 users. These very early adopters will help publicise the benefit of this approach so that by 2017-2018 deployment will be much wider – around 600 users.

In order for the clinical acceptance to proceed there will be a number of developments in other areas. Already hospitals are starting to outsource complex data management and adopt more ICT-based solutions. By 2014-2015 there will be available integrated digitised medical records in countries leading in adoption of EHR systems by hospitals such as Finland, Sweden, and Denmark, thus enabling e-consultations between GPs, radiologists, gastroenterologists, for patients with chronic GI diseases. Sharing primary care records electronically with hospital specialists asynchronously at times convenient to each will enable more informed clinical decision making and reduced outpatient referrals.

By around 2014 business models for ICT model-based approaches to diagnosis and disease management will have emerged and be beginning to be tried out in various healthcare systems. By 2022 the concept of the 'Super Patient' will be well established in the area of management of chronic diseases in a distributed healthcare environment. Super patients are those well informed individuals who take advantage of online tools and services and can manage their health and illnesses better via collaborating with healthcare providers and peers. The role of the super patient is more prominent in the case of chronic diseases, and health systems will actively pursue mechanisms to facilitate their involvement. This is a dramatic change from the current practice where patients are passive recipients of medical care and have little or no role to play in deciding and managing their own treatment plans should they get sick. Healthcare occurs primarily when patients enter the healthcare building and stops when they exit. For many years, this has been the only model possible and therefore healthcare and medicine has been a locally delivered activity. A new finance model to pay for this new approach to healthcare, likely one in which the patient pays, is expected by 2022.

The changes in approach to healthcare delivery brought on by the use of ICT-based solutions such as the VPH models will add further momentum to the shift in emphasis in healthcare from hospitals towards community-based care where the option of large expensive equipment is not affordable.

By 2018 it is expected that there will be international agreement emerging on VPH standard interfaces. This will allow greater integration between VPH models of related organ systems thus paving the way for a more effective VPH-based approach. By 2018 at least one further organ system model will be integrated with the VIGOR++ model for the GI tract. By 2020-2022 the VIGOR++ model will have been integrated with at least three other organ system models.

⁴The Economist, Frugal healing, Jan 20th 2011, <http://www.economist.com/node/17963427>

By 2022 there will be large scale genetic screening programmes for high-risk people and this identification of predisposition will encourage further adoption of these VPH tools for monitoring in programmes of disease prevention.

Clinical work flows will develop continuously to accommodate the evolving needs of making use of such VPH tools and the first dedicated work flows to accommodate the VIGOR++ tools will have emerged by 2015. Scientist interested in epidemiology of the GI tract diseases will benefit from the advances in Geographic Information Systems (e.g. Google Earth, Virtual Earth, and Terraserver) which can be used to identify risk factors for disease and targets for preventive medicine after studying distribution and patterns in various populations.

2.4 Products, processes and services

The roadmap foresees the proliferation of applications making use of an individual's or a population's GI data. These efforts are to be of small scale but will gain momentum and create ecosystems. A range of disease management tools, clinical research management tools, wellness applications, complemented by social networking tools covering popular medical conditions are to follow.

In terms of the products, processes and services to be delivered, the VIGOR++ tools will be the first in a new line of VPH related tools of relevance to diseases of the GI tract.

The first VIGOR++ toolbox will be delivered during 2012-2013 with a second version ready by the project end in 2014. By 2014 a new Crohn's Disease Severity Index will be proposed, which will be a major improvement on current practice by being quantifiable and accurate and starting to be commonly used.

Standards for models and data will have been established by 2014. A prototype system will be delivered in 2014 followed by clinical trials and approvals through 2015 and 2016. Beyond 2014 genetic information will begin to be considered alongside the clinical evaluations. Market introduction will happen around 2016-2017. The system will be adopted by doctors and their patients by around 2018.

With the appropriate level of investment, the VIGOR++ tools will have been further developed to address ulcerative colitis by 2015-2016, functional GI disorders by 2017-2018 and bowel cancer by 2020-2022. Development of the model for the different diseases will be enabled by the development of different protocols rather than the use of different imaging modalities. Such protocols cover for example the differences in the magnetic field and the patient preparation take a long time to change. For the bowel this is a VIGOR++ deliverable so is expected by 2014.

Services will be increasingly delivered by remote clinicians and other experts. Currently remote and offline examination of medical records is already happening but remote and real time processes will emerge shortly. In addition, new workflows will need to be created suitable to allow the 'Super Patient' to manage their own health. This work flow design is beginning to happen across some departments in the health systems but still needs to be addressed across major healthcare systems.

Factors to determine the rate of adoption of the aforementioned products, processes and services within the healthcare systems include:

- Accuracy (reliability of methodology)
- Efficiency (workflow)
- Usability (accessibility)
- Cost performance
- Sustainability

2.5 Technology

Several technologies underpin the development of ICT tools for GI diagnosis and disease management. This section describes some of the key developments anticipated in the next decade. It covers developments supporting medical fields, notably radiology and gastroenterology, but is also tightly linked to developments in non-medical fields, such as telecommunications. The layout of this section maps the different technical work packages of the VIGOR++ project.

Clinical care and research increasingly rely upon digitised patient information. This information is stored in patient records, laboratory reports and medical images. Among the most prominent technology trends is the shift from Picture archiving and communication systems (PACS) to cloud computing. PACS has been instrumental in supporting data migration and data backups, fault tolerance and security but importantly cloud computing reduces significantly the need for capital investments in ICT infrastructure. It has just started making its way to medical imaging starting with the most data processing intensive applications such as advanced visualisation and CAD. Cloud computing also enables commercial software enterprises to share data, applications and components with scientific and clinical communities. Important privacy issues exist when using cloud computing as data is now stored on IT infrastructures outside the hospital. Potential risks for privacy breaches are when an individual on the staff of the cloud vendor who can gain administrative access to a server and potentially access data. Also, the data owners do not necessarily know where that data is stored. A solution would encrypt all data from end to end. There are also related regulations such as auditing according to which at any particular time a hospital or health care organisation needs to know who can potentially have access to data. Generally, the healthcare industry has been slow to embrace cloud computing. This is especially true among the smaller medical practices.

Radiology is a multi-technology-driven and inherently metadata-intensive specialist area of medicine. Effective interpretation of the ever growing amounts of data has recently renewed the interest in the application of machine learning techniques for predicting disease severity.

2.5.1 Image Analysis

The global medical imaging industry is primed to experience significant growth through the next decade. Medical imaging can be categorised into the following main modalities: x-ray, ultrasound, computed tomography (CT), magnetic resonance imaging (MRI), positron emission tomography (PET), single photon emission tomography (SPECT), mammography and fluoroscopy. Globally, x-ray is the most frequently used imaging procedure, MRI is second, and PET, SPECT, CT and nuclear medicine follow. PACS and contrast agents are the sub-segments in medical imaging market that have grown significantly in recent years. As a result of these medical imaging advancements, the multi-slice systems are generating large volumes of data, and this creates demand for data storage, 3D visualisation and analysis.

MRI, which does not expose patients to ionising radiation, is distinguished by its superior capacity to resolve soft tissue details – ideal in the context of the GI tract. No other non-invasive technique offers clinicians the opportunity to visualise morphology and pathology with such exquisite spatial resolution. Ultrasound has locally higher spatial resolution, but the window is limited and comparing examinations and communicating results (esp. in the case of complex findings) is cumbersome. Using MRI detailed structures can be distinguished with great accuracy, offering clinicians a critical benefit for detecting and characterising diseases. MRI helps clinicians differentiate normal tissues from pathology based on disparate soft tissue relaxation rates or even based on functional variations between tissues. Furthermore, MRI is the modality of choice in follow-up examinations to visualise disease recurrence or in monitoring the impact of interventions. The market for MRI systems includes low-field, mid-field, high-field, open and intra-operative MRIs. A low-field system is defined as any system below 1.5 Tesla,

while mid-field is 1.5 Tesla and high-field is 3.0 Tesla. Low-field systems are being replaced by mid-field and high-field systems due to the enhanced image quality of these devices. Installations for low-field MRIs are expected to significantly decline over the next 10 years.

Importantly, MRI is not a static technology, particularly as it pertains to soft tissue imaging. As physicists and radiologists continuously probe the potential of MRI physics and how they can be harnessed for imaging purposes, we expected evolution of image quality based on scanner output (resolution/contrast/noise). From an MRI perspective improvements in sequences will make it much more rapid. Currently, it takes 30-50 min to scan the whole abdomen but with fast sequences it is anticipated that the whole abdomen will be scanned with high quality in one breath-hold within the next 5 years. It is already possible to perform imaging the complete abdomen in one breath-hold, but the image quality is less than for sequences that lasts longer. Data resolution will improve from current 4-6 mm thickness to 1-2 mm thickness as has been demonstrated for 3D T1w sequences which already provide thin slices. In 10 years' time, it will start to approach the resolution of CT but not actually meet it. In 10 years' time it will be possible to do a full scan of the small bowel in 10min with the new protocols. There may be some improvement due to coil developments however these are unlikely to be mainstream or widely used. The move to stronger magnets actually brings its own problems due to the heterogeneity in the field e.g. going from 3.5T to 7T or 9.4T would bring in all sorts of artefacts from fluids and gases in the abdomen so it is unlikely that 7T would be used for the bowel (although they find their way in brain scans). In 10 years' time radiologists and gastroenterologists will realistically be using the same scanner platforms. The sequence design however is likely to evolve to bring the biggest improvements. This will result in lower acquisition times due to software improvements.

Changes due to the use of different contrast agents are a possibility but likely to be only just emerging. Contrast agent use will likely always be needed but the specific contrast agents to be used may be modified in the future. Some are currently being developed in animal models. The timeline to human use is very long though and may just emerge for specialised application e.g. for fibrosis detection in the 10 year time frame. It is worth bearing in mind that not all hospitals have the capability to do MRI of the small bowel (in the UK for instance less than 38% have such capability). Given that it takes 10-15 years to introduce new protocols, it is unlikely that radiologists will be moving to new protocols within the next 10 years.

Advances in nanotechnology and molecular imaging that may be applied in multiple imaging modalities present unique opportunities for combined imaging approaches. Combined PET/CT systems are used clinically, although radiation exposure and limited soft tissue contrast remain limitations. Improvements in PET-MRI in particular may have an impact on GI imaging as they can provide complementary information on metabolism and anatomic detail with high spatial resolution. However, such research so far has been conducted with live animals.⁵

Reconstructing images of the GI tract is challenging since it is a large, mobile organ with many turns and overlapping regions. There are huge registration problems as there are so many different data volumes. Where different structures have similar threshold density, it can become impossible to separate them simply by adjusting volume rendering parameters. The solution is called segmentation, a manual or automatic procedure that can remove the unwanted structures from the image. VIGOR++ has been investigating registration of bowel data and further improvements are to be expected here. Work is also being undertaken in adapting existing image analysis algorithms to accurately measure descriptive properties of GI wall tissue. Current VIGOR++ research algorithms (not optimised for speed) are taking up to 10 min for registration and segmentation of a study. In 10 years' time though this should be real time or

⁵ Linda A. Jelicks, Imaging the Gastrointestinal Tract of Small Animals, *Journal of Neuroparasitology*, Vol. 1 (2010).

close to it. Commercial algorithms are closer to real time in other applications e.g. artery segmentation.

Regarding fundamental techniques of image processing, compressive sensing may enable faster scanning protocols in the near future. Compressive sensing offers high resolution image reconstruction from a small number of uncorrelated measurements.

Tools are also being developed by various image processing groups for energy minimisation. More work is needed on measuring features and particularly on measuring wall thicknesses or layers. This requires correlating a priori information into the registration scheme. There is work going on now in neurosciences where they are targeting sequences to the structures. This enables them to best pick up the histological features of a specific tissue e.g. fibrosis or cellular infiltrates. There are issues of how to combine all of this data e.g. diffusion weighted image, T2, T1, pre- and post-contrast agent. By the end of 10 years we will see the new sequences developed even if they are not in common clinical use.

It is anticipated that there will continue to be a lot of separate weighing up of lab findings relative to the imaging findings. It is an open research question how to map laboratory data onto the images. There will be registration problems across different modalities, if one was to implement a usable zoom in and out function. There is work going on in the colon (much simpler structure than the small bowel) to correlate CT colonography with endoscopic data in real time. However, this is an enormous technical challenge. Hence, effective correlation may happen but not in the next five years. In VIGOR++ it is expected that if a user clicks on the inflamed areas the scores for the predicted endoscopy will be called up.

Standards help both users and vendors develop approaches for integrating various medical imaging and information systems. Among such standards DICOM is widely adopted for its ability to interface workflow and electronic health record systems. DICOM is considered adequate from a clinician's perspective and it is unrealistic to expect a change in the dominant formats given that multiple areas of clinical practice are using them. Developers do not find DICOM to be efficient for storage and manipulation of data but work with it anyway due to its acceptance in the clinical environment. To overcome limitations during development they tend to extract to NIfTI which includes important information like the orientation of the image and is better for easier manipulation etc. but can't store much metadata. Joint working groups e.g. DICOM/ HL7 will contribute to future standard extensions. Vendors shouldn't underestimate the importance of accepted standards – if anything new does come along it would still have to be backwards compatible with DICOM.

2.5.2 Modelling and classification

From an algorithmic point of view, more accurate and detailed modelling of the GI tract is a realistic prospect. These models will be partly based on statistical processing of static and dynamic images of normal and pathological population studies via machine learning. Machine learning builds on recent progress in algorithms and theory, growing amounts of online data and increased availability of computational power. Machine learning tools can discover patterns in medical data to provide support for the decision-making processes in many healthcare areas, including screening, diagnosis, prognosis, monitoring, therapy, and hospital management. Key functions include association detection, classification and data mining. Tools used for performing such functions include Bayesian and nearest neighbour classifiers, neural networks, support vector machines and decision trees. All these tools depend greatly on the availability of large data sets.

Among the forms of learning (i.e. unsupervised, supervised, reinforcement) supervised learning is better suited to the different development stages of the GI tract modelling and classification

tasks. This is because initially only small and imbalanced training sets may be available but over time the size and quality of these data sets will improve.

Further, with MRI images it is difficult to have unsupervised learning due to the high level of similarity between different regions. In future it should be possible to include a feedback step in the context of reinforcement/active learning when sufficient data is available for the system to make well informed estimations and where an expert can verify correct or incorrect identification in order to speed up the labelling process.

Several use cases may be supported: for instance when expert identify regions of interest and then the system tries to determine if there is disease or not in those. Statistical features coupled with the segmentation information will enable the formation of feature vectors characterising the different regions. Comparing such feature vectors locally and globally will help establish disease severity, such as the CDEIS score for Crohn's.

Classification results depend on how much data the system has been trained with. This may hinder quick acceptability for clinical practice as clinicians as well as regulators such as the MHRA or FDA wish to minimise variability in quality.

It is possible to try and mimic the expert i.e. follow radiologists while they annotate images and find out which features they implicitly look at in images (e.g. shape, intensity, possibly a combination of these, in a neighbourhood of a region). Feature selection algorithms (i.e. removing irrelevant and redundant features from the data to automatically establish the feature subsets that lead to better classification results) is a field of research still requiring further attention. The ability of the random forest classifier to cope with feature selection has been indicated by the first results within VIGOR++. Another option is to use each feature in a separate classification and then combine outputs of separate classifiers (i.e. voting) to come up with better classification.

Classification speed in the context of GI tract diagnosis is not a major issue (unlike with image analysis). For the data sets examined so far it is quite fast (10min to cover all samples). Processing the images takes much more time. It is also not a big obstacle in combining outputs of different classifiers. Potentially with larger feature sets or with genomic feature sets classification may become an issue. Speed is of course more of an issue during the training phase although there is still scope to optimise the code further.

Classification could become a bottleneck if reinforcement learning was used to retrain the classifier during use. It is the training rather than the classification that is time consuming.

Speed would be increased dramatically though if pixelwise classification could be performed. Currently the approach is grouping slices into superpixels however in the future, with higher computing power; the superpixel may increase in size adding more contexture/neighbourhood information.

It would make sense to standardise the superpixel definition to work across clinics with different images. Indeed, it would be good to have an algorithm that segments whole images into supervoxels as part of a standardisation step. Different hospitals could have different volumes represented. It remains to be determined experimentally how many supervoxels would serve the task well.

Assuming a cloud-based deployment, pre-processing needs to have been performed off-line to speed-up retrieval when using thin clients (e.g. for the case when a user wishes to retrieve from databases studies with similar extend of a disease). Superpixels can play a key role in adding contextual information to underpin such data retrieval tasks. A practical problem maybe that some manual intervention in the form of some input by user / annotations may be still required. Another unknown factor is establishing how reproducible systems will be using data sets from different scanners. It is hoped that future tools will be robust enough to cope with such hardware

variability. Nevertheless, it is realistic to expect that by 2018 doctors will be able to use the tools to compare the evolution of disease amongst patients.

2.5.3 Interactive Visualisation

There are two types of visualisation – information visualisation and scientific visualisation although the trend is to do away with this separation. The two communities do however still exist rather separately. Medical data can be effectively visualised through a variety of methods creating abstractions of greater sophistication from the raw data, permitting the display and manipulation of complex data.

Advanced 3D visualisation integration with Picture Archiving and Communication Systems (PACS) has become an essential component of clinical applications. Nowadays, almost every PACS vendor is offering basic 3D functionality, such as Maximum Intensity Projection (MIP) and Multiplanar Reconstruction (MPR). Further, the PACS vendors are acquiring or entering into partnerships with imaging technology companies to provide the 3D integration. A trend has emerged towards lighter, handheld and portable 3D imaging equipment. The focus is towards improving the diagnostic procedure by improving quality of images and providing superior imaging services at comparatively lower costs.

Research is required in combining visualisations comprising imaging and non-imaging data (e.g. text from patient records, microscopy data, blood/air flows inside human organs). This covers the issue of how to simultaneously display both 3D and 2D information or descriptive and image data. Clearly simultaneous display of such data is only sensible if they are correlated. One option is to make the visualisation interactive by moving the cursor over some 3D volume and further information or some other type of representation pops up at the appropriate locations. There is already much work in labelling (display text on surfaces on volume rendering). Many combined techniques are now used in ‘hypothesis generating visualisation’. New techniques are emerging for generating the hypotheses.

Despite the advances in hardware, including supercomputers, medical data sets are typically huge and do not fit into GPU memory. Hybrid GPU and CPU will be available in 5-10 years. It is known that Intel for instance is working on this. However, investments in this domain have failed to live up to the expectations so far. New techniques are needed to load and visualise such data sets. Medical data pose a significant problem of data transfer within hospitals – I/O times are the dominating factor. Multi-resolution solutions have become the much cited requirement for visualisation. If the data set is so big that it can't be easily moved then the visualisation system can run on a data centre. It is a matter of selecting just the right data from within a huge data set. There is a trend in image analysis towards compressed sensing, according to which signals are represented on a sparse basis. Whilst this is now also being discussed with regards to visualisation it is yet to be adopted. Researchers in the visualisation community have not so far dedicated effort to implement the mathematics of it and it remains to be seen how applicable the technique may therefore be.

As long as there is a continued need to display large data sets in hospitals there will be a trend to larger displays. This is particularly useful for examining fine details. However, efforts to incorporate gigapixel displays may be wasted effort in this field as they start to exceed the eye's ability to see. Nano-projectors may offer a good alternative solution, assuming that the issues of powering them can be resolved. Mobile devices will be useful in some instances but the processing power in these devices will not improve dramatically so rendering will still need to be done elsewhere. The solution is to have the data sets and the rendering power hosted elsewhere and to just move the final images around. This is already done in the VIGOR++ project using the 3DNet platform.

For high quality volume rendering one needs good segmentation as several features will have the same intensity. There are techniques to 'peel off' layers of opaque rendering but this is an artificial rendering style solution where the problem should rather be solved in segmentation.

New research is needed for the effective visualisation of multi-valued data e.g. clinical studies where patients are frequently examined with different medical imaging modalities (multi-modal visualisation techniques). The most important issue here is image registration. Once correspondence is known then one can visualise by fusing many data sets to produce relatively few. Specific registration techniques are available and should be compared for effectiveness. Registration is a major field of research with lots of work particularly for brain images. For the effective visualisation in a GI tract model there are several challenges, particularly relating to the shape variability through flexing of the component organs. GI imaging is not usually isotropic and in most cases data comprises both thick and thin slices. It is not clear when in the future we can expect a reasonable solution to what is a difficult problem. Instead of major breakthroughs in this area it is more likely that there will be improvements as a result of advances in the image acquisition protocols. It is already possible for the clinician to observe linked time series data however the accuracy of matching up images is only good enough for an overview. The individual observations are still better where accurate detailed information is required.

A number of steps are needed to realise multi-scale visualisation of the GI tract. Data at different scales should not have too much of a gap between them so as not to lose coherence. There will be large/wide domain images plus more specific areas where much smaller scale detail is available. For instance, systems should enable the users to zoom in and out across histopathology and MRI data. Registration issues, e.g. precise location of sampling, are paramount for the successful implementation of such operation.

Virtual and mixed reality methods in medical visualisation have been the subject of projects for almost a decade. This has involved the use of real-time, stereoscopic displays and direct user interaction thus enabling better understanding of the 3D environment in less time. Virtual reality (VR) has been used in hospitals for planning of surgery and was popular with some clinicians where they had to deal with very complex spatial issues. However, the whole set up is technologically too complex for many doctors so its use was prohibited in hospitals. In fact, there is still scepticism that it actually helps surgeons operate better or quicker. In general the feeling is that for diagnosis the added value is not as high as for surgery, although one strong possibility is in locating the affected part of the GI. 3D surgical systems are used mainly in brain research but do not see much use in diagnosis e.g. in radiology. For VR to have an impact in medicine the value proposition must become stronger or the cost of systems must decrease very significantly – otherwise it will always struggle to become mainstream.

2.5.4 Capsule Endoscopy: A Complementary Technology

A technology that may prove to be both complementary with the VIGOR++ tools as well as an alternative approach in some cases is that of capsule endoscopy.

Capsule endoscopy involves a pill-sized, video imaging wireless capsule that is swallowed by the patient. Each capsule contains a camera, light-emitting diodes, batteries and a wireless transmitter. During the procedure the patient can move freely around, and over 50,000 colour images are recorded for around 8 hours onto a data-recorder worn on a belt around the patient's waist. The capsule passes through the small intestine as peristalsis occurs and is excreted naturally by the patient.

So that the images are clear, the patient will be asked to prepare for the test, by fasting, taking laxatives, or a combination of both. The technology is already widely used in many hospitals with many millions of procedures having been carried out to date.

Capsule Endoscopy serves as an additional diagnostic tool for patients who have been suffering from GI disorders, such as bleeding, without a definitive diagnosis using other techniques e.g. Gastroscopy, Colonoscopy and Enteroscopy. It is used to examine parts of the gastrointestinal tract that cannot be seen with other types of endoscopy i.e. the majority of the middle portion of the GI tract, the small intestine. It can also be used to evaluate conditions of the small bowel that cause diarrhoea, pain or weight loss, such as Crohn's Disease that involves the small bowel. It is also useful in assessing the polyps in the small intestine. Wireless capsule endoscopy is sometimes recommended in cases where the diagnosis of Crohn's disease is known but it is necessary to determine the extent and severity of small bowel involvement and whether active inflammatory lesions exist in the setting of a functional bowel disorder.

Claimed benefits include:

- the capsule is small and so easily swallowed
- the procedure is painless and sedation free
- the patient is mobile
- there is no exposure to harmful radiation
- patients go home later the same day

Disadvantages include:

- it is relatively expensive and is not always fully reimbursed
- viewing of images is very time consuming for the clinician
- some people find it difficult to swallow
- there is a risk of the camera getting stuck in narrow areas of the bowel e.g. strictures, thus requiring surgery for removal. This is particularly an issue in cases of Crohn's disease where luminal narrowing is common. One study found capsule retention in 13% of patients with known Crohn's. Risk of impaction is still around 1% even when patients with known strictures are avoided.
- it is not suitable for people with gastroparesis – a condition that reduces the ability of the stomach to empty its contents but where there is no blockage
- unlike MRI it does not provide information on wall thickness or any other information beyond the visible surface
- as passage through the GI tract is uncontrolled it is not possible to investigate in any more depth than what is captured visibly on the pass through

Capsule endoscopy products include PillCam (Given Imaging), EndoCapsule (Olympus), Sayaka (RF Systems) and MiroCam (IntroMedic).

The Robotics for Healthcare roadmap⁶ for smart medical capsules suggests that the key areas of innovation for future development relate to being able to measure and to manipulate the capsule more. These include:

- Extension of what can be measured e.g. through other sensors beyond visible cameras
- An ability to control the movement of the capsule either through an external magnetic force field or through its own propulsion or an ability to anchor the capsule at a required location using micro-hooks. This will require realtime location of device position.
- Smart targeted drug delivery from a capsule
- Ability to take biopsy samples and potentially even carry out more complicated small surgical procedures such as removing unwanted tissue

⁶Robotics for Healthcare, for the EC DG Information Society, Butter et al., Dec 2008

The Robotics for Healthcare roadmap is rather optimistic in terms of timescales for these innovations to be delivered having anticipated that some would be beginning to be available by now. Here we re-estimate timescales based on indications from information on those currently developing such solutions.

Extension of sensing capabilities is in progress and will continue to deliver results from around 2014 onwards. There is currently work in progress on control of capsule movement with microgripping and magnetic movement approaches likely to deliver solutions over the period 2013-2015. More sophisticated propulsion systems are some way off and likely to only start to be delivered towards the end of our roadmapping period i.e. around 2018-2022. Smart drug delivery is feasible and should be technically possible relatively soon (possibly 2013) but actual delivery of solutions is likely to take much longer as this will be highly regulated (2018-2022). Likewise with biopsy and microsurgery which probably will not be available until around 2018-2022.

The speed of uptake of innovation in these areas is likely to be primarily limited by the time to implement changes in the complex and highly regulated field that is medicine and healthcare.

The key enabling technologies which must be developed to realise the innovations above include:

- Miniature multispectral imaging cameras
- Very small and energy efficient biomedical sensors beyond pH, temperature and conventional cameras to lab on a chip
- Localisation technologies to aid more accurate mapping – probably including the ability to use capsule in MRI scanners so requiring construction from advanced non-magnetic materials
- Advanced human-machine interfacing to allow surgeons to control the capsules manually
- Mobile energy systems to extend operating lifetime for more detailed examinations or interventions, including energy harvesting and use of energy sources in the body e.g. biofuel cells
- Advances in mechatronics to equip the capsules with microgrippers and MEMS-based propulsion systems

2.6 Other resources required

Europe's science and engineering education is of high standard providing a strong platform of theoretical knowledge and research capability with the potential to support industry. It is important, however, to ensure that the future needs for skills and capabilities are discussed and provided for.

2.6.1 Training

Clinical staff need to be trained on the use the novel ICT tools that are becoming an increasingly ubiquitous part of their working environment. Part of this training will come from lectures and seminars that they will need to carry out as part of their continuous professional development. Some of newest ICT platforms, e.g. those based on cloud computing, provide opportunities to carry out training at convenient locations and at different times in their working schedule. They allows them to interact with other clinical professionals engaged in similar training, and thus to acquire understanding of the novel tools deployed without losing the collaborative interaction that is important in learning or being distracted from their main role in healthcare.

As the trend towards inter- and multi-disciplinarity grows, common international education standards will be required. This will become increasingly important as researchers, scientists, doctors and patients work in virtual teams. At the same time, mobility of researchers and scientists is critical. Common education standards will facilitate work done within such virtual teams and mobility.

Health economics is becoming a critical area in public policy, in academia and in the private sector, with a shortage of qualified specialists at postgraduate level. Many more professionals with an analytical skill-base will be required in the next 5 to 10 years to evaluate and improve the efficiency and effectiveness of GI related systems.

2.6.2 Business models

As with the introduction of any new working practice or technology into healthcare systems there is a need to consider the implications of cost and benefit. A change such as that brought about by the deployment of VPH type approaches is also likely to require further thinking on the appropriate business models to deal with these new costs.

The VPH community, as represented by the VPH Network of Excellence, has recognised the need for appropriate business models to ensure that the benefits of VPH technology becomes viable and a beneficial alternative to current medical approaches⁷. They do not however make suggestions as to what business models might be appropriate. Instead they suggest that it is too early to specify distinct models and that work is required in analysing the market, business potential and exploitation strategies. They do note that a disruptive approach such as VPH may face the need to overcome some significant vested interests.

At the heart of the issue for the adoption of VPH approaches, and indeed any new technology, is that the national health systems are under severe financial pressure with funding and therefore service is strictly rationed. The standard reimbursement model for healthcare is no longer considered sustainable. Increasing healthcare costs, increased lifespans with associated chronic illness and increased expectations of care have strained the model to breaking point. There may be cases where the benefit and cost savings of the tools are clearly demonstrated and incorporated into standard health service provision. However, it is more likely that other approaches will be required to extract greater value and therefore remove further cost from the current payers – the national healthcare systems.

The deployment of ICT solutions in healthcare such as electronic health records is already underway and is aimed at lower costs and better connectivity of information across the current silos of healthcare. However, much of the deployment to date is in the form of pilot studies and little appears to have been done to develop scalable business models for new approaches to ICT delivered healthcare.

There are already efforts to reduce the costs of healthcare by providing hosted solutions on a subscription and seat-based model and some efforts towards a pay per use model. This is seen in the area of x-ray radiology. Improved information architecture and consolidation of storage capacity has made remote management and manipulation of high quality images possible where real time transmission is not required. This is already prompting consideration of patient owned data and consent models to deal with the questions of how you get consent for other use, how assurances on use can be given and how you incentivise sharing of image data.

There is a trend to increased consumer power and extent of choice in health and wellbeing but high industry fragmentation is resulting in disconnected engagement. There is a lack of sustainable business models to cover the long term chronic disease management. For the lower risk health and wellbeing type services there is already an acceptance of a consumer pays

⁷A Vision and Strategy for the VPH, 2011.

market. At the other extreme with the very high risk emergency type healthcare or medical intervention the current healthcare market is established and functional with the NHS for example paying. It is between these two extremes in the area of disease management that the lack of sustainable business models is most noticeable. What is emerging is a complex ecosystem of relationships between all sorts of service providers and healthcare organisations. This set up is not optimised and does not do much to reduce cost of ownership or ensure good reuse of information and assets.

The future is likely to include the involvement of an intermediary hosting service perhaps run by large ICT contractors where issues such as data warehousing, identity management, payments and billing, electronic health records, data analysis and decision support etc are all dealt with. This opens up opportunities for new business models which recognise who creates and appropriates value from the new ICT-based services.

So what could all of this mean for VIGOR++ and its successors? It is possible that the hosts of such ICT services may be able to sell access to digital patient information by performing a brokerage role thus covering or subsidising the costs of the service. Payers may include the patients themselves or insurers where healthcare is private. The government, through its national health system, may be a part-payer of the costs of the hosted solution or may support individual access through personal health budgets. There may even be revenue streams from pharmaceutical companies wishing to access data from large patient databases for medical research and drug development.

In an ecosystem with many interested parties it is quite possible that a mixed business model may exist to extract revenue from various stakeholders. An advertising based model would derive revenue from the potential to sell treatment or other targeted offerings to patients. A subscription model where the patient pays may support a more patient centric future giving the option of allowing access to multiple service providers for additional services or second opinions. The subscription model also works well for selling access to the information on large patient groups e.g. for pharmaceutical companies. In e-commerce subscription and advertising models are often combined.

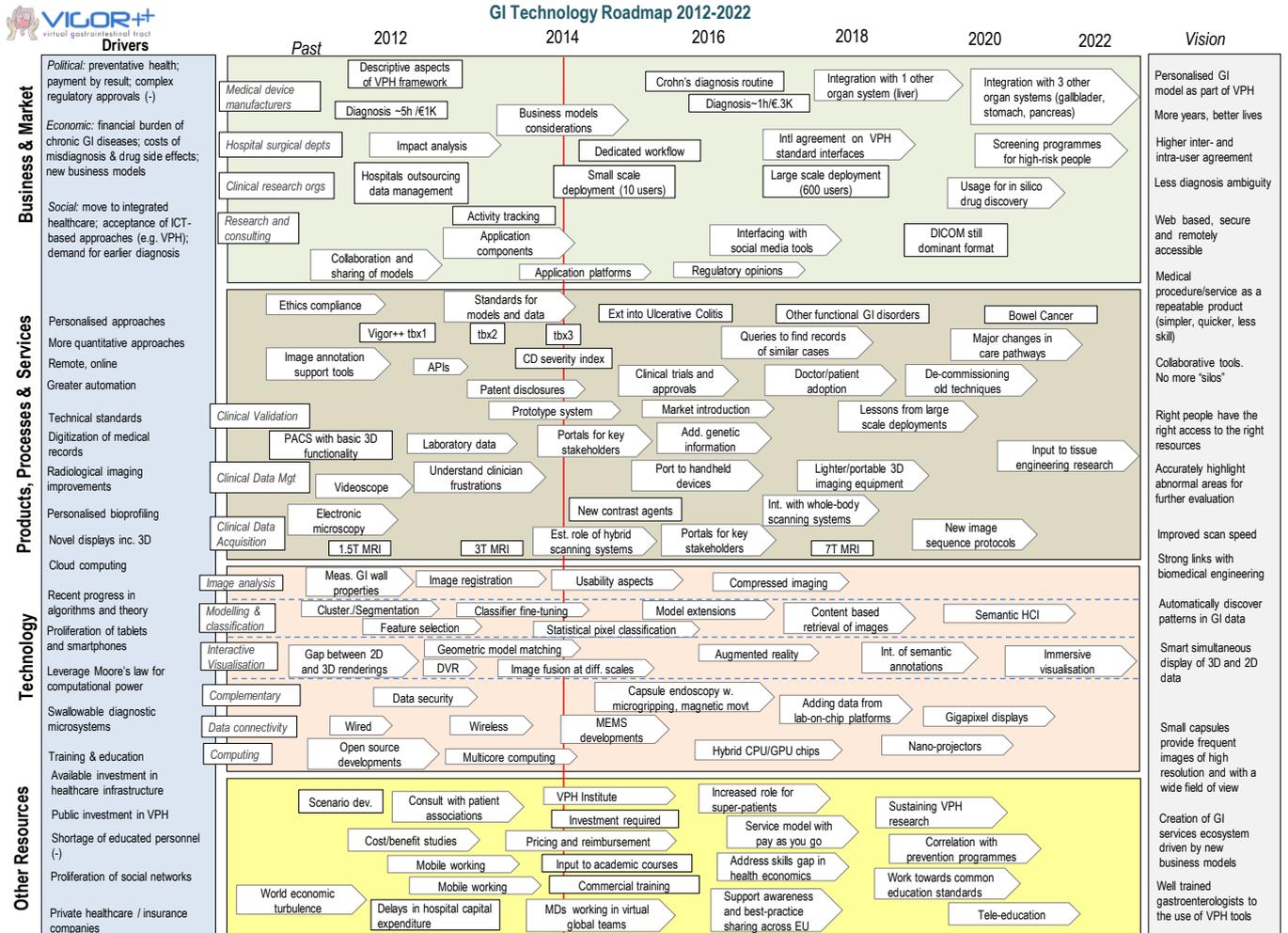
Much work is still required to explore the value of the information provided by VPH to both the patient and to other potential users. There have been no shortage of pilot efforts to explore ehealth services but what these have not done is address the challenges of running a full scale system. There has even been recognition of models drawn from other sectors such as banking and utilities. What is required though is leadership to implement a radical change in the face of a pressing need. Issues that will need to be addressed in order for a VPH-like tool to be widely deployed in healthcare include:

- Ownership of digital health records
- Data privacy
- Methods for providing consent for use and assurances on that use
- Vendor neutral image archiving
- Incentives to overcoming the vested interests of the status quo

2.6.3 Social media

The quality of communication in consultations needs to be vastly improved. According to the recent EFFCA survey 53% of patients feel that they were not able to tell the specialist something that was important, and 65% say they wish they were asked more probing questions. Social media already plays an important role in providing essential support for GI sufferers and is likely to be important for the future adoption of VIGOR++ type tools. It allows people from all over the world to meet, share experiences and support each other in many novel ways. The relevant communities are underpinned by mutual understanding, shared values and behaviours.

2.7 Roadmap 2012-2022 (in graphical form)



3 Concluding Remarks

The roadmapping exercise would suggest that there is a reasonable expectation that the vision of a GI tract model updated using individual's MRI scans for diagnosis and management of GI diseases can be realised over the next 10 years.

Several drivers are well aligned to encouraging this to happen. National health systems are faced with huge challenges in dealing with the consequences of an ageing population and increased prevalence of long-term chronic diseases as well as greater expectations of healthcare. This is happening at a time when budgets are restricted and means that new more efficient and effective healthcare solutions are required. It is also supported by a shift in focus from hospital-centred reactive healthcare to a more patient-centric preventative approach. There is a growing recognition that diseases of the GI tract are a major healthcare issue in the developed world. Doctors need more advanced tools for effective and quantifiable detection and disease management and ICT-based tools are becoming more viable, particularly with the advent of cloud computing solutions.

Technology advances in a number of fields are also likely to help drive the realisation of the vision. These range from improvements in image quality via better resolution MRI and improved sequence design through to new techniques for image registration and segmentation which should help deliver multi-scale imaging products. Compressive imaging and cloud computing will support more efficient and powerful solutions. Advances in machine learning techniques will support better modelling and classification.

Business and market highlights anticipated include:

- integrated digitised medical records across healthcare systems by 2014/15
- large-scale screening programmes for high-risk people by 2022
- Crohn's disease diagnosis using VIGOR++ model will be routine by 2016 and the model integrated with other related organ models by 2022
- the cost and time of diagnosis will be reduced from €1k / 5hrs now to €300 / 1hr by 2016
- small scale deployment (20 users) from end of VIGOR++ (2014) but large scale deployment (600 users) by 2018
- de-commissioning of old techniques and radical change of care pathways (2018-2022)
- an increased involvement of well-informed patients (so called Super Patients) in their own healthcare choices facilitated by ICT-based solutions

Anticipated product or service highlights include:

- workflows developed to accommodate large-scale screening and to enable the 'Super Patient' to manage their own health
- industry increasingly accessing clinical and patient opinion via social media to improve product and service design
- remote and offline examination evolving to remote real-time diagnosis
- automation at various stages of the protocol enabling increased speed of diagnosis
- integrated VPH models, linking Crohn's / GI disease models to cancer of the bowel and then extended to other cancers
- use of the tools for '*in silico*' drug discovery before 2022
- new finance models being developed to pay for this new approach to healthcare with a range of service models including recognition of the opportunity to target several potential customer types
-

Some technology development highlights that will help realise the vision include:

Image analysis

- high quality full abdominal scan in 10min by 2022 (approx. 30-50 min today)
- resolution to improve from 4-6mm to 1-2mm thickness by 2022 for a wide range of MRI pulse sequences
- image quality and utility improvements from changes to sequence design
- significant further work needed in the area of selecting and combining features and in addressing registration problems
- image processing to be improved by energy minimisation tools and correlation to a priori information
- optimised algorithms will enable near real-time image segmentation and registration
- multiscale image correlation will continue to be a major challenge that won't be fully addressed by 2022
- DICOM will continue to be the dominant format

Modelling & classification

- supervised learning will be most suited to developing the GI model
- expert user involvement to identify regions to be classified and expert feedback to improve classifiers will continue for the foreseeable future
- furtherwork will be needed on feature selection – e.g. wall thickness, textures, shapes, signal intensity, edge features as there is a need for good large sets of representative features
- classification speed will not be an issue for run time (training is what takes time) until genomic feature sets become incorporated
- on-going research will determine the optimal size/structure of superpixels/voxels which are useful for feature extraction, capture redundancy, and reducing complexity of processing tasks.
- statistical features coupled with segmentation information will help calculate the CDEIS score and compare evolution of disease amongst patients

Visualisation

- significant research will be needed to address image fusion at different scales e.g. when using different medical imaging modalities
- there will be combined interactive visualisations where you can move a cursor over a 3D volume to call up further clinical information – probably the CDEIS scores
- new techniques will emerge to deal with the representation from huge multi-dimensional data sets e.g. the trend to compressed imaging or similar will impact in the visualisation field
- mobile device use will be enabled by generating the visualisations at data centre thus only needing to transmit the final image
- augmented- and mixed-reality methods are still in their infancy but are likely to be used in niche applications including training of new physicians and radiologists

With the major drivers of the market, products and services and the technology development trends appearing to favour the likely realisation of the vision set out in this roadmap, it is the widespread implementation aspects that seem least certain. In order to extract maximum benefit from this new approach to healthcare it is anticipated that new business models will be required.

While there is plenty of inspiration from examples such as e-commerce for designing such models it is clear that the biggest challenge will be overcoming the inertia and vested interests of current practices. The economic, political and social drivers may all be pushing in the same direction but one should never underestimate the challenge of changing the way major national health systems operate. It is likely that initial progress will be made in isolated areas and initiatives with consolidation of approach coming as the benefits to all stakeholders are more clearly demonstrated and quantified. Patient groups and associations and the use of social media all have a role to play in encouraging this transition. The situation may also be helped by efforts to understand what benefits all potential stakeholders could gain from the information in this ICT enabled healthcare toolset and what value they would put on such information. Only then can the incentives for all be realised.

Personalisation of healthcare will enable higher quality of treatment and therapies and empower patients. Implementation of personalised medicine will require creating new legal and ethical frameworks, health insurance policies and education. ICT will affect all aspects of people's personal and work lives, breaking through today's social and cultural norms. Issues of privacy, trust and security will gain importance.

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5 List of frequently occurring acronyms

3D	Three Dimensional
AMC	Academic Medical Center, University of Amsterdam
CDAI	Crohn's Disease Activity Index
CDEIS	Crohn's Disease Endoscopic Index of Severity
CPU	Central Processing Unit
CT	Computed Tomography
DICOM	Digital Imaging and Communications in Medicine
DVR	Direct Volume Rendering
EFCCA	European Federation of Crohn's and Ulcerative Colitis Associations
HER	Electronic Health Record
ETHZ	Eidgenössische Technische Hochschule Zürich
GPU	Graphics Processing Unit
HL7	Health Level Seven
IBD	Inflammatory Bowel Disease
FDA	Food and Drug Administration (USA)
ICT	Information & Communication Technologies
GI	Gastrointestinal
MHRA	Medicines and Healthcare products Regulatory Agency (UK)
MIP	Maximum Intensity Projection
MPR	Multiplanar Reconstruction
MRI	Magnetic Resonance Imaging
NifTI	Neuroimaging Informatics Technology Initiative
PACS	Picture archiving and communication system
PET	Positron Emission Tomography
SPECT	Single Photon Emission Tomography
UC	Ulcerative Colitis
UCLH	University College London Hospitals NHS Foundation Trust
VPH	Virtual Physiological Human
VR	Virtual Reality
ZIB	Zuse Institute Berlin