B CORE TOPICS 2014

B 1 RESEARCH AND INNOVATION IN UNIVERSITY MEDICINE

B 1–1 ON THE IMPORTANCE OF MEDICAL RESEARCH

In recent decades, ground-breaking scientific discoveries in the fields of genetics and molecular diagnostics have generated waves of new developments and revolutionary changes in medical care. However, from the perspective of patients and doctors, medical research has also contributed to the development and dissemination of expensive medication and treatment methods. Life expectancy has risen over recent decades and an ageing population has increased the demand for healthcare services. At the same time, these developments have led to a strong increase in expenditure within the national health services worldwide, significantly exceeding economic growth in the respective countries. Table 2 shows the growth in healthcare expenditure for selected OECD countries for the period from 1970 to 2010. In Europe, it has nearly doubled from 4.9 percent to 9.6 percent as a share of GDP. This development also applies to Germany, France, the Netherlands and Switzerland, which currently spend 11 to 12 percent of their GDP on health. In the United States, the percentage of GDP expended on healthcare has increased from 7.1 percent to 17.6 percent in the same period.

In 2006, the Federal Government included the policy areas of health research and medical technology in its High-Tech Strategy, not least as a consequence of the social and financial importance of healthcare.[132] The new legislative period will also require important decisions to be made concerning the design of policy measures in these fields.

In recent decades, expenditure on medical research has increased even more strongly than that on healthcare. The United States has been in the vanguard of this development. Here, both the budget for basic biomedical research and the R&D expenditure of the pharmaceutical industry for biotechnology and medical technology have been increased considerably (cf. Table 3).

Between 1982 and 2012, US public and private R&D expenditure taken as a whole increased from USD 10 billion to USD 130 billion annually. The growth in the budget of the National Institutes of Health (NIH), the most important state organisation for biomedical research in the United States, was especially expansive. The annual funds of the NIH grew from USD 3.9 billion to USD 31 billion between 1980 and 2012 (with a GDP of USD 16.2 trillion).[133] Compared with the level of state funding in Germany, this represents a considerable difference. In total, Germany funded medical research to the tune of EUR 780 million in 2012 (with a GDP of EUR 2.7 trillion), of which EUR 287 million went to project management bodies within the German Aerospace Center (DLR) and EUR 493 million to the German Research Foundation (DFG).[134]

It is only in recent years that the United States' health research budget has been cut again due to limits on public funding resulting from increased healthcare and medical research costs. In Germany, health expenditure as a percentage of GDP has risen continually over recent years, however, it has not reached the US level.[135]

Development of healthcare expenditure as a proportion of GDP in selected countries 1970–2010

TAB 02

DATA DOWNLOAD

	National healthcare expenditure as a percentage of GDP				
	1970	**1980**	**1990**	**2000**	**2010**
Germany	6.3	8.4	8.3	10.4	11.5
France	5.7	7.0	8.4	10.1	11.7
Great Britain	4.5	5.6	5.8	7.0	9.6
Japan	4.6	6.4	5.8	7.6	9.6
Canada	7.0	7.0	8.9	8.8	11.4
Netherlands	7.2	7.4	8.0	8.0	12.1
Switzerland	5.4	7.2	8.0	9.9	10.9
USA	6.9	9.0	12.4	13.7	17.7
OECD	**5.3**	**6.6**	**6.9**	**7.8**	**9.6**

Source: own depiction based on OECD Health at a Glance 2013 (data for 1980 – 2010) and OECD Health at a Glance 2001 (data for 1970).

Development of R&D in the pharmaceutical industry in selected countries 1980–2010

TAB 03

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	R&D expenditure in the pharmaceutical industry (in million USD PPP)				Growth p.a. 2000–2010	Percentage share of R&D expenditure in BERD
	1980	**1990**	**2000**	**2010**		
USA	1,777	6,287	12,793	49,415	14.5	17.7
Japan	742	2,647	4,811	11,351	9.0	10.6
Great Britain	496	2,003	4,475	6,945	4.5	28.6
Germany	528	1,263	2,315	4,609	7.1	8.0
France	322	1,179	2,557	3,762	3.9	11.9
Switzerland	–	–	991	2,988[4]	14.8	38.6
Belgium	–	238[1]	652	1,506[3]	9.7	11.6
Spain	–	192	355	1,002	10.9	9.6
Canada	–	204	621	549	–1.2	4.4
Denmark	–	144	610[2]	916	4.6	19.4

[1]1992 [2]2001 [3]2009 [4]2008
BERD: business enterprise expenditure on research and development
PPP: purchasing power parity
Source: own depiction based on OECD MSTI 2013/1 and OECD ANBERD 2009.

B 1–2 THE CENTRAL ROLE OF UNIVERSITY MEDICINE

University medicine is of central importance to the performance of medical research, as it is here that the link between healthcare provision and medical research is established. At the university hospitals both basic research and patient and hospital-related research is conducted, and thus the translation of research results into healthcare practice (see Box 3). In particular, clinical studies and initial trials are conducted at university hospitals. Furthermore, university hospitals are also responsible for the training of physicians and the training of young researchers. In recent years, research into rare diseases and their treatment, as well as the development of individualised medical treatment measures have gained in importance. Pharmaceuticals are being developed for ever smaller patient cohorts.

BOX 03

Translation and translational medicine

Basic scientific research is becoming increasingly important for clinical treatment. Translational medicine as a link between basic research (bench) and clinical application (bedside) is playing an increasingly important role. The key expression "from bench to bedside" defines the act of establishing a bridge between the knowledge of biological processes and new human diagnostic techniques and therapies. However, this does not simply imply a one-sided stimulation of clinical applications by basic research – it is equally the case that their implementation in patient-specific situations provides an important stimulus for basic research.

Yet, the process of translation within medical research is time and cost-intensive. Few insights gained in the laboratory are actually deployed in clinical praxis. In order to promote and expand translational research, it is also necessary to improve communication between researchers and physicians and feed knowledge gained from clinical applications back into laboratory research.

Over recent years, translational medicine has gained in importance and the focus of national research policies has increasingly shifted to the optimisation of translation processes.

Research in the university medicine sector increasingly calls for cooperation between various research disciplines. In particular, cooperation between medical professionals and scientists is becoming increasingly important. In order to guarantee the necessary interdisciplinarity, flexible forms of inter-institutional collaboration are of advantage. This presents university hospitals and their cooperation partners with new challenges.

B 1–3 INTERNATIONAL COMPARISON OF UNIVERSITY MEDICINE LOCATIONS

A comparison of the best performing university medicine locations from five countries strong in research – Germany, the Netherlands, Canada, Switzerland and the United States – has shown that Germany has competitive locations, however, none of them are ranked amongst the top locations internationally.[136] The United States have by far the best performing university medicine locations – defined as the respective universities together with the university hospitals and teaching hospitals, respectively (cf. Table 4). The US locations have the best publication performance and generate more patents than the research locations in the comparison countries.

These results are drawn from a study conducted by the Frauenhofer Institute for Systems and Innovation Research (ISI), commissioned by the Expert Commission. The goal of the study was to identify the strongest university medicine research locations worldwide and compare them with each other.[137]

Figure 11 shows the absolute number of publications per location as well as the publication intensity of the authors at the respective locations for 2012. Publication intensity is calculated by dividing the number of medical publications by the number of authors active at each location.[138]

The university medicine location with the highest level of publications is Boston/Cambridge with Harvard University and the associated university hospitals. The dominance of the Boston/Cambridge site is not just apparent in terms of absolute figures, but also in terms of publication intensity. The German sites, measured in terms of absolute number of publications as well as publication intensity, are generally ranked in the middle of the comparison group.

Overview of university medicine locations

TAB 04

DATA DOWNLOAD

Location	Institutions	Country
Berlin	Freie Universität Berlin, Humboldt Universität Berlin, Charité	DE
Hanover	Hannover Medical School, University Hospital	DE
Heidelberg	University of Heidelberg, University Hospital Heidelberg	DE
Munich	LMU Munich, TU München, University Hospital Munich	DE
Tübingen	University of Tübingen, University Hospital Tübingen	DE
Basel	University of Basel, University Hospital Basel	CH
Bern	University of Bern, University Hospital Bern	CH
Geneva	University of Geneva, University Hospital Geneva	CH
Zurich	University of Zurich, University Hospital Zurich	CH
Amsterdam	University of Amsterdam, Vrije Universität Amsterdam, University Hospital Amsterdam	NL
Leiden	University of Leiden, University Hospital Leiden	NL
Rotterdam	University of Rotterdam, University Hospital Rotterdam	NL
Utrecht	University of Utrecht, University Hospital Utrecht	NL
Hamilton	McMaster University, Hamilton Health Sciences - Chedoke McMaster Hospital	CA
Montreal	University of Montreal, McGill University, University of Montreal Hospital Centre, Montreal General Hospital	CA
Toronto	University of Toronto, University Health Network (Princess Margaret Cancer Centre, Toronto General Hospital, Toronto Western Hospital, Toronto Rehab)	CA
Vancouver	University of British Columbia, UBC Hospital	CA
Baltimore	Johns Hopkins University, Johns Hopkins Hospital	US
Boston/Cambridge	Harvard University, Massachusetts General Hospital - HMS (Harvard Medical School)	US
Houston	University of Texas, Houston, University of Texas Health Science Center at Houston	US
San Francisco	University of California, San Francisco, UCSF Medical Center	US
Washington	University of Washington, University of Washington Medical Center	US

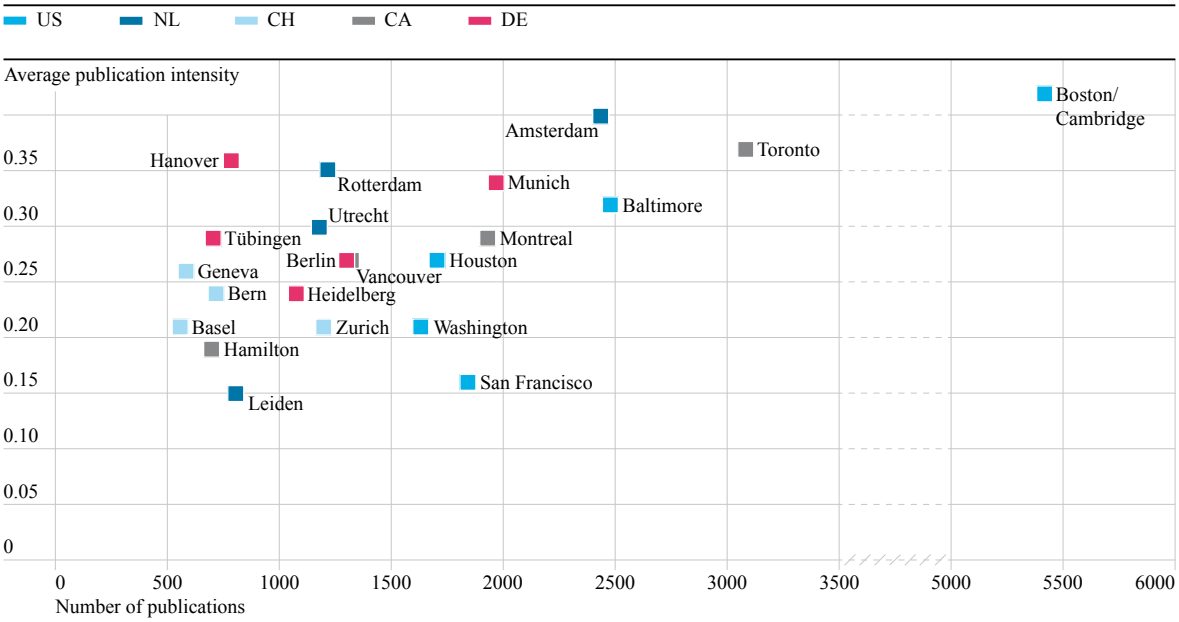
The above mentioned university medicine locations were selected on the basis of an analysis of the publication output. To distinguish between university publications and university hospital publications, the affiliations captured in the publications have been used. The publications of the affiliated university hospitals were captured as university hospital publications when the respective university was specifically included as an affiliate, or when the name of the respective city and the term "hospital" were mentioned as affiliates. For instance, publications of the Technical University of Munich's university hospital *Klinikum rechts der Isar* were assigned to the location of Munich when the respective publications mentioned the Technical University of Munich or the city of Munich under the author's affiliates.
Source: own depiction based on Frietsch et al. (2014)

This applies in particular to the locations of Heidelberg, Berlin and Tübingen. In terms of publication intensity, Munich and Hanover belong to the leading group. Although Munich exhibits a higher absolute number of publications than Hanover, Hanover has the highest publication intensity of all the German locations.

Figure 12 shows the excellence rate for the respective locations in 2010. The excellence rate is calculated as the percentage of a location's publications within the top 10 percent of cited medical research publications. This indicator is primarily designed to measure research excellence, i.e. the focus is on the quality of the publications from the respective locations. The highest excellence rates within the university medicine sector were achieved by US locations, above all Boston/Cambridge, followed by San Francisco and Houston. The only non-American location ranked in the leading group for this indicator was Rotterdam, followed by Baltimore and Washington. The German locations were generally ranked at

FIG 11 **Number of publications and publication intensity of locations in 2012**

DATA DOWNLOAD



Publication intensity: average number of publications per author.
Source: Web of Science, Scopus, calculations by Fraunhofer ISI.

How to read: in 2012, the authors active at the research institutions of the Boston/Cambridge location published 5,425 publications. On average this amounts to 0.42 publications per author (publication intensity).

the bottom of this comparison group. The exception here is Heidelberg, which achieved a middle ranking. Although quantitatively the Heidelberg site published less than the other German university medicine sites – both per capita and in total – it appears that Heidelberg had many publications of a higher quality compared with other German locations.

Overall, this indicator points to a highly country-specific picture. With a few exceptions, the highest excellence rates were achieved by the top locations in the United States, followed by the Netherlands, Canada, Switzerland and Germany. Yet, it should be noted that publications in US periodicals generally feature more frequently in the top 10 percent of cited publications worldwide, which, at least in part, accounts for the resulting ranking. It is probably still easier for authors from the United States to publish in a US periodical than it is for authors from other countries.

Figure 13 shows the number of transnational medical patent applications for the respective locations in relation to the average number of patent citations per application within the period 2005 to 2007. In addition to the quantity of applications, the qualitative dimension is also represented, measured in terms of the average number of patent citations within a three-year period. Patent citations are one of the most frequently used indicators for the quality of patents employed in academic literature.[139]

It is clear from the diagram that, on average, patent applications from the Utrecht location have a very high technological significance. The same applies to patent applications from the San Francisco, Washington and Harvard locations. The Swiss locations of Basel, Bern and Geneva also display very high values for this indicator. This is followed by a large middle field composed of locations from all countries with an average of 1.5 and two citations per patent application. German tertiary education institutions – led by Heidelberg – are situated in this middle field.

Figure 14 shows patent and publication intensity for the respective locations during the 2008 to 2010 period.[140] It is clear from the diagram that the Boston/Cambridge site not only occupies the top position with respect to the selected patent indicator,

Excellence rate of publications per location in 2010

FIG 12

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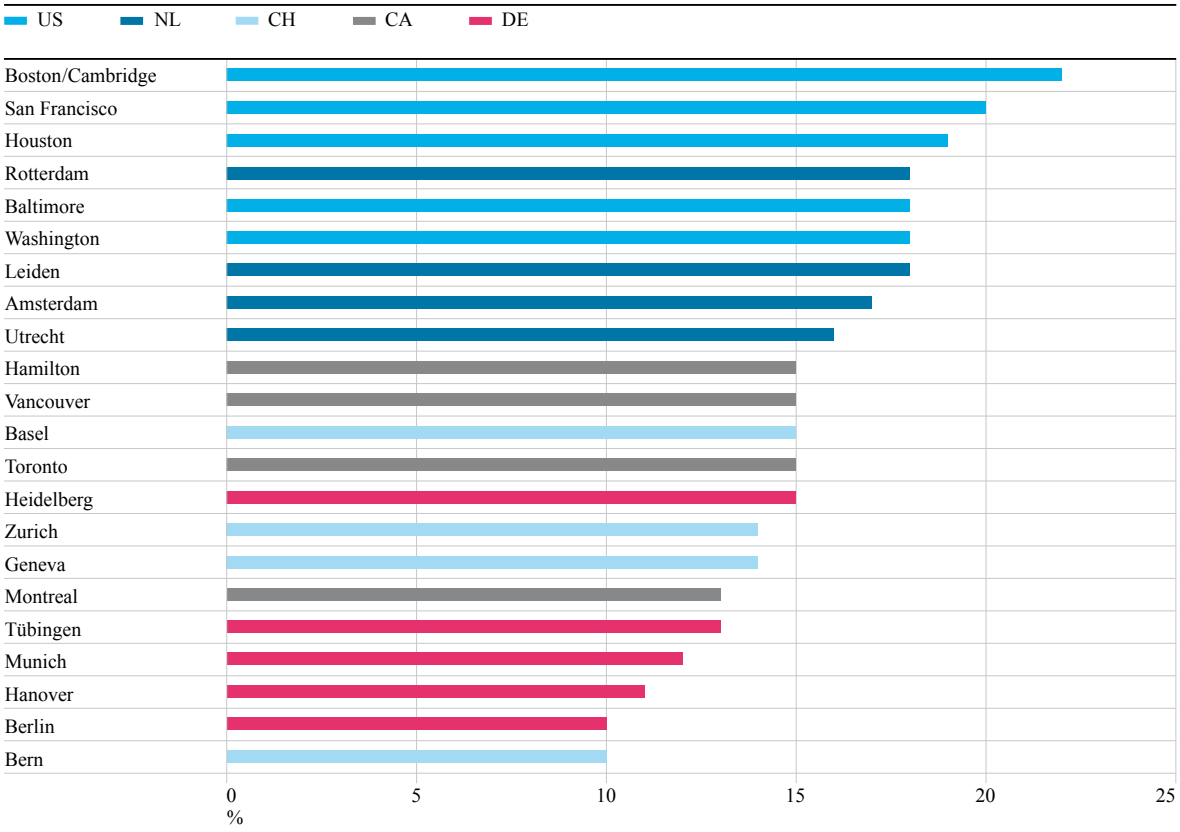

Excellence rate: share of a location's publications that are among the top ten percent of the world's most frequently cited publications in medicine, relative to all medical publications of the respective location.
Source: Web of Science, calculations by Fraunhofer ISI.

How to read: in 2010, 22 percent of medical publications published by authors active in the location of Boston/Cambridge were among the top ten percent of the world's most frequently cited medical publications.

but also displays the highest publication intensity by far. The Munich site displays a relatively high patent and publication intensity, being ranked third for patents and fourth for publications within the comparison group. The Basel, Bern, Berlin, Heidelberg and Baltimore sites also demonstrate a relatively high patent intensity. However, they tend to be ranked in the middle field in terms of publications. Overall, it is clear that the respective locations have diverse profiles, pursuing both scientific publications and patent applications as opposed to concentrating exclusively on the one or the other.

The comparative study documents the dominance of the Boston/Cambridge site with Harvard University and the associated hospitals in the field of biomedical research. The Boston/Cambridge site not only produces more biomedical publications and patents than all the other locations worldwide, it is also the leader in terms of the quality of results and the productivity of the researchers and inventors. German locations are ranked in the middle field in terms of patents and publications as well as productivity. German locations score less well in terms of research quality measured according to the publication excellence rate. A further improvement in scientific performance should therefore be primarily focussed on the quality of these research contributions.

FIG 13 **Number of transnational medical patent applications and average number of patent citations per application 2005–2007**

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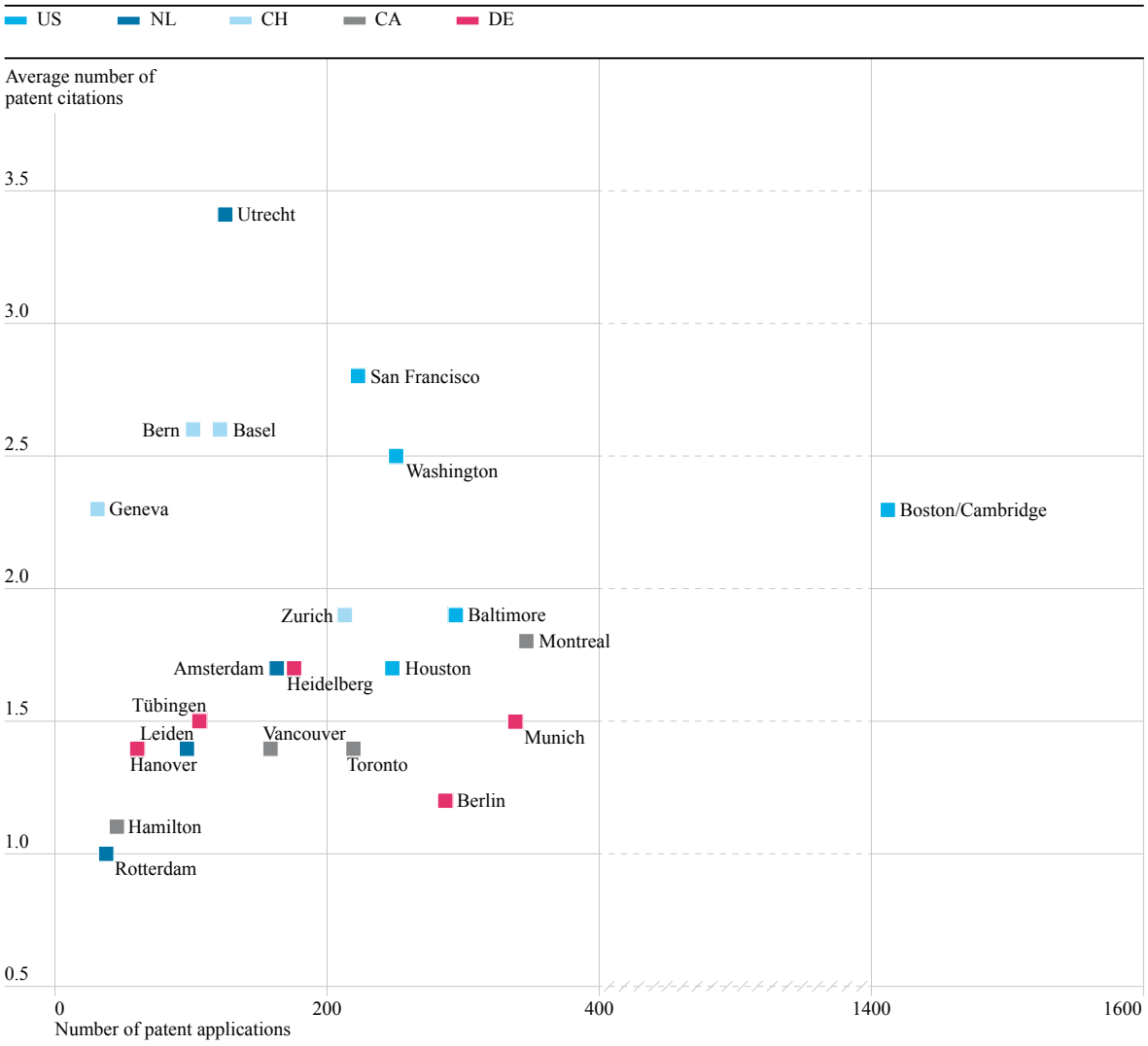

Source: EPA - PATSTAT, calculations by Fraunhofer ISI.

How to read: between 2005 and 2007, 1417 transnational medical patents were filed by scientists active at the location of Boston/Cambridge. On average, each of these filed patents was cited by subsequent patents 2.3 times within a period of four years.

B 1–4 ORGANISATIONAL FRAMEWORK OF MEDICAL RESEARCH

The funding of medical research is organised differently internationally

The funding of medical research in Germany, as in other countries, is characterised by institutional complexity. The following comparison of the funding structures in Germany, Canada, the Netherlands, Switzerland and the United States provides an overview of the most important institutions for the financing of medical research as well as the institutions which conduct medical research. Current changes in the funding structure in Germany are analysed against this background. While funding in the United States, Canada and the Netherlands is primarily administered by independent institutions which in some cases are explicitly responsible for medical research, in Germany public funds are awarded by administrative organisations that do not have any specific medical focus. These intermediary organisations are the

Patent and publication intensity of locations 2008 – 2010

FIG 14

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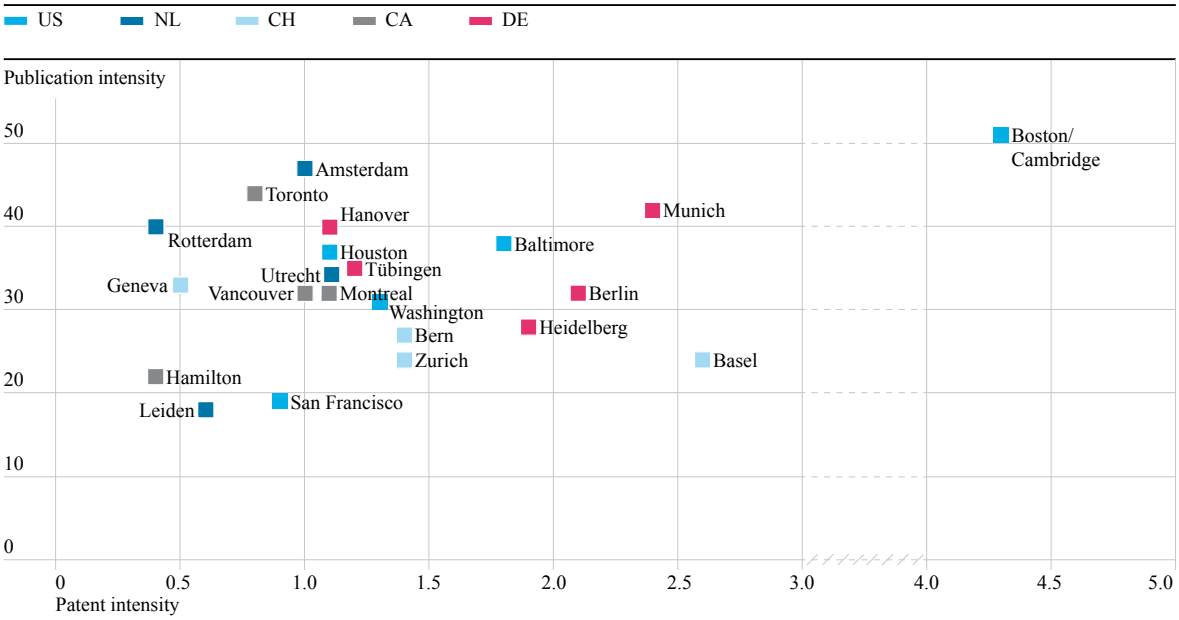


Patent and publication intensity: number of transnational patent applications/publications per 100 authors.
Source: Web of Science, Scopus, EPA - PATSTAT, calculations by Fraunhofer ISI.

How to read: between 2008 and 2010, an average of 51 publications and 4.3 patent applications per 100 publishing scientists (authors) was recorded for the location of Boston/Cambridge.

German Aerospace Center (DLR), which as project management body administers the awarding and coordination of research funds on behalf of the Federal Ministry of Education and Research (BMBF), and the independent German Research Foundation (DFG) financed by the Federal and *Länder* governments.

In the comparison countries the institutions responsible for medical research, such as the National Institutes of Health (NIH) in the United States or the Canadian Institutes of Health (CIHR), are under the auspices of the respective health ministries. While these ministries function as funding bodies, they delegate the execution of this task to the responsible funding institutions, which are frequently also responsible for strategy development and the implementation of coordinated, topical funding in the field of medical research.[141]

In Switzerland, public research funding is the responsibility of the Swiss National Science Foundation (SNF), which acts on behalf of the federal government. The national foundation awards funding for the medicine/biology sector but does not undertake any research activities itself.[142]

An essential feature of the German research system is the separation between funding and research institutions. The DLR, which operates at the behest of the BMBF and the BMG, and the DFG, operate as funding bodies but do not conduct any R&D activities themselves. This institutional separation is justified on the grounds that it helps to prevent conflicting goals in the perceived role of the scientific establishments. The DFG is concerned that equitable cooperation between different research facilities would be made more difficult if one of the cooperation partners had to apply to the other for the funding required for the cooperation.[143]

The separation between funding and research institutions established in Germany does not exist in the United States or Canada, or in the basic research sector in the Netherlands.[144] In the United States, the NIH also carries out its own research. In 2012 the NIH invested around USD 5.7 billion of its total budget in its own research projects; the vast majority, to the sum of USD 25 billion, was awarded to projects outside the NIH. While the CIHR in Canada and the Nederlandse Organisatie voor Wetenschappelijk Onderzoek (NWO)[145] are primarily responsible

BOX 04

Boston/Cambridge as a centre of life sciences and innovation

The Boston/Cambridge region, like no other location worldwide, displays excellent framework conditions for successful medical research. With more than 100 universities and colleges, Boston/Cambridge is the intellectual stronghold of the east coast. It has ca. 4.5 million inhabitants and in 2012 generated an economic output of almost USD 340 billion.[146] In addition to the top universities of Harvard and the Massachusetts Institute of Technology (MIT) in its immediate proximity, the region of Boston/Cambridge is also home to further renowned private universities (Boston University, Northeastern, Tufts, Boston College, Brandeis University, etc.) and state universities, such as the University of Massachusetts. The academic landscape of the Boston/Cambridge region is enhanced by the renowned teaching hospitals of the Harvard Medical School and Boston University (Beth Israel Deaconess Medical Center, Brigham and Women's, Children's, Massachusetts General Hospital), which for years have occupied a pole position with respect to research funding from the National Institutes of Health (NIH). In addition, the Boston/Cambridge region is also home to highly renowned research institutes such as the Whitehead Institute, the Broad Institute, jointly run by Harvard University and MIT, the Dana-Farber Cancer Institute, belonging to Harvard Medical School, and the David H. Koch Institute for Integrative Cancer Research. A further important research institute is the Draper Laboratory, which mostly conducts research work commissioned by the Ministry of Defense.

In addition to the extraordinary density of universities, hospitals and research facilities, nine out of ten of the world's largest companies from the biotechnology and pharmaceutical industries have a presence in Boston, including the global research centres of Novartis, Merck and AstraZeneca. The origins of the formerly venture capital-backed companies such as Biogen Idec and Genzyme (Sanofi) are also found here. Furthermore, the corporate side, in particular the transfer of research findings into new products, is strengthened by the presence of numerous venture capitalists.

A focus of these Boston-based institutions is translational medicine, i.e. the rapid implementation of scientific knowledge in clinical practice.[147] The close cooperation required for this is made considerably easier by their immediate proximity to one another. Many of the institutions named are in fact within walking distance of each other.[148]

The research institutions located in Boston/Cambridge are continually experimenting with new forms of cooperation. In the field of cancer research for instance, the David H. Koch Institute provides an institutional framework for the interdisciplinary cooperation of engineers and biologists with MIT scientists from different specialties. This cross-disciplinary approach is also the focus of the "Bridge Project" initiated by the Koch Institute and the Dana-Farber Cancer Institute. The aim is for teams composed of scientists from different specialties to think beyond traditional scientific networks and thus identify new paths for cancer research.

A similar interdisciplinary approach is also pursued by the Broad Institute. Formally connected to the MIT, Harvard University and the associated hospitals, the Broad Institute links the work of students, postgraduates, scientists and administrative specialists in its own research projects. The institute's three organisational units (core member laboratories, programs and platforms) are characterised by a regular interdisciplinary exchange and the bundling of cross-disciplinary expertise.

for the awarding of funding to external research institutions, they can also conduct their own research projects at the affiliated institutes.[149]

A similar approach was first adopted in Germany with the establishment of the German Centres for Health Research (DZG) in 2009. Thus, the Helmholtz institutes integrated into the DZG are entrusted with research tasks as well as assuming responsibility for administering funds for the other participating research institutes.[150] However, in distinction to the institutions named above, the focus of the Helmholtz Association (HGF) is the conduction of its own research. In terms of volume, the administration

Boston/Cambridge and its major medical research institutions FIG 15

Universities

1 Boston University
2 Harvard University
2a Harvard Medical School
3 Massachusetts Institute of Technology
4 Northeastern University
5 Tufts University School of Medicine

Research institutes

6 Broad Institute
7 Dana-Farber Cancer Institute
8 David H. Koch Institute for Integrative Research
9 Draper Laboratory
10 Whitehead Institute for Biomedical Research

Teaching hospitals

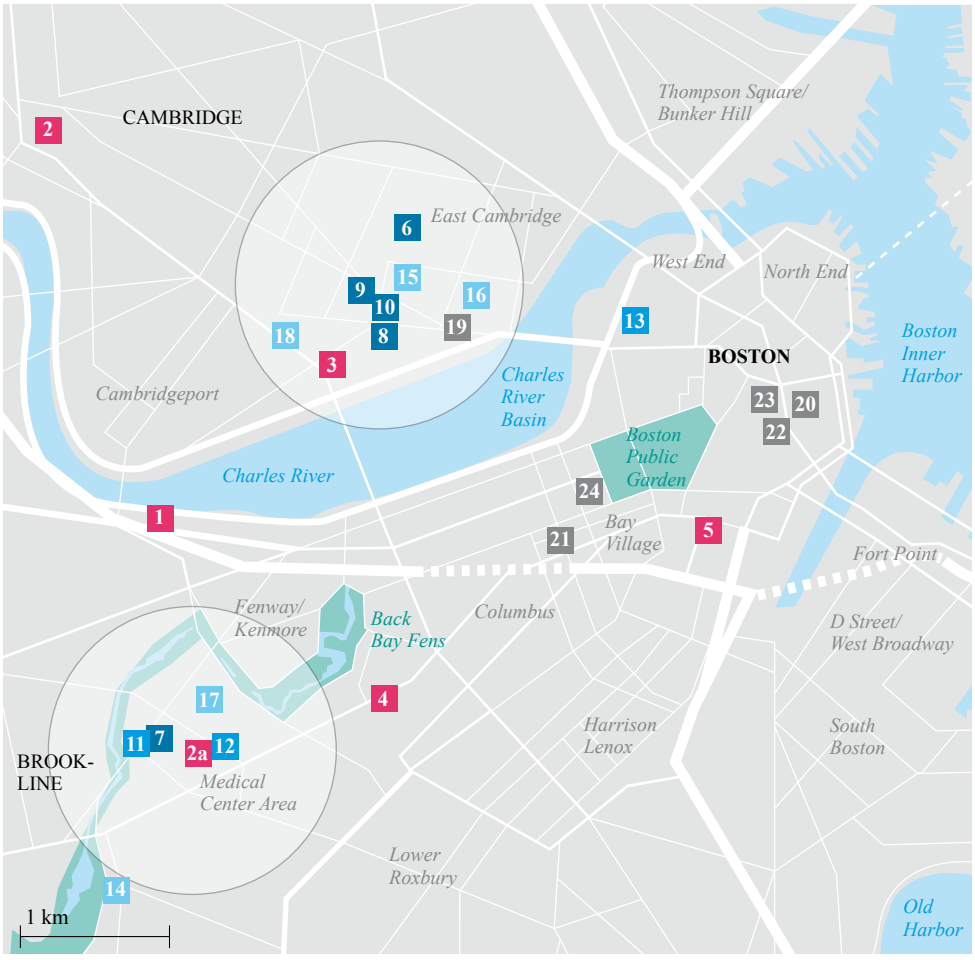
11 Beth Israel Deaconess Medical Center
12 Brigham & Women´s Hospital
13 Massachusetts General Hospital

Companies

14 AstraZeneca Hope Lodge Center
15 Biogen Idec
16 Genzyme Corporation
17 Merck Research Laboratories
18 Novartis Institutes for Biomedical Research

Venture capitalists[151]

19 Clarus Ventures
20 Morgenthaler Ventures
21 MPM Capital
22 Needham Funds
23 Schroder Ventures Life Sciences
24 Third Rock Ventures



Source: own research.

of external projects only constitutes a small part of its work.

In addition, measures have been taken to limit potential conflict between the tasks of research and research funding. Thus, during the establishment of the DZG the Helmholtz institutes were not involved in the process of selecting the other facilities. The selection of all the facilities incorporated in the DZG was carried out by the BMBF and the DLR in collaboration with an external evaluation committee. In the opinion of the Expert Commission, these measures have initially succeeded in preventing the feared conflict of interest.

However, in its position paper "Helmholtz 2020 – Shaping the Future Through Partnership", the HGF suggests that institutional funding should be more closely linked to project funding, proposing the conduction of its own project funding activities as a means to achieve this.[152] The Expert Commission rejects this idea (cf. Chapter A 1), as a mandate extended in this fashion would upset the well-balanced division of roles established between non-university research organisations and the universities, to the detriment of the universities.

The different funding practices of the German funding institutes DFG and DLR

With the DFG and the project management organisation DLR, working at the behest of the BMBF and the BMG, Germany has established a complementary structure for research funding that is unique worldwide. However, the funding practices of the two institutions display a number of distinct features. While the BMBF/DLR conducts programme-oriented research funding organised according to strategic goals (top-down), the DFG primarily funds basic research in which the researchers themselves select the research topic (bottom-up).

Funding from the BMBF/DLR is often described by universities and non-university research organisations as more bureaucratic than that from the DFG. In many cases, funding by the BMBF/DLR is associated with more complex research specifications and more elaborate controlling procedures.[153]

While there may be objective reasons for the increased administrative requirements,[154] the Expert Commission calls for the identification of any tendencies towards excessively bureaucratic handling of funding instruments by the funding organisations, and their limitation.

Furthermore, researchers active in the university medicine sector complain that in the case of BMBF/DLR financed research projects – in contrast to DFG financed projects – it is difficult to meet the requirements with respect to a clear division between research activities and patient care. In principle the DFG, just like the BMBF/DLR, also demands that research and patient care times be listed separately. That said, the practical implementation of these requirements is considered to be less strict and comparatively unbureaucratic with DFG projects.[155]

Promoting translation through new forms of cooperation

To improve the translation of results, university hospitals collaborate with private enterprises and non-university research organisations.[156] Forms of cooperation extend from cooperation on individual research projects, institutional cooperation in larger funding contexts – such as special research fields, the excellence initiatives and the German Centres for Health Research – through to the partial fusion of the participating institutions. Thus, from 2015 onwards, cooperation between the Charité and the Max Delbrück Center for Molecular Medicine (MDC) will be conducted within the framework of the newly founded Berlin Institute of Health (BIH), a public corporation.[157]

The six German Centres for Health Research currently form a framework for cooperation between university medicine and non-university research organisations. These centres are designed to offer optimal conditions for research into major widespread diseases in Germany, while also promoting cross-institutional cooperation in health research. Thanks to their integrative structure, they help to network researchers from universities and non-university research organisations working in the field of major widespread diseases. This networking and the associated expansion of existing research structures for translational research, together with the close interaction

TAB 05

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German Centres for Health Research (DZG)

Name of centre	Year established	Number of locations	Organisations-form	Administrative office	Fund administration
German Center for Cardiovascular Research (DZHK)	2010	7	registered society	Autonomous (Charité)	Max Delbrück Center for Molecular Medicine (Helmholtz)
German Center for Infection Research (DZIF)	2010	7	registered society	Helmholtz Centre for Infection Research	Helmholtz Centre for Infection Research
German Center for Lung Research (DZL)	2010	5	registered society	University of Giessen (University Hospital Giessen and Marburg Lung Center, UGMLC)	Helmholtz Zentrum München
German Consortium for Translational Cancer Research (DKTK)	2012	8	foundation	German Cancer Research Center (DZKF) Heidelberg (Helmholtz)	German Cancer Research Center (DZKF) Heidelberg (Helmholtz)
German Center for Diabetes Research (DZD)	2009	5	registered society	Helmholtz Zentrum München	Helmholtz Zentrum München
German Center for Neurodegenerative Diseases (DZNE)	2009	9	Helmholtz Centre + cooperation partners (registered society)	DZNE location Bonn (Helmholtz)	DZNE location Bonn (Helmholtz)

Source: Loos et al. (2014: 168).

with the corporate sector, are designed to facilitate a more rapid transfer of research results into everyday clinical practice.[158]

In the period up to 2015, the six centres that have been established since 2009 will receive BMBF funding totalling EUR 700 million. The Federal Government provides 90 percent of the funding, while the remaining 10 percent come from the federal states participating in the DZG.[159]

Even though the DZG have chosen different organisational forms and different cooperation structures, a feature they all share is the management of funds by the participating Helmholtz centres. Four of the DZG have also located their administration offices in a Helmholtz centre. The prominent role of the Helmholtz Association relative to the university partners has been widely criticised.[160] The Federal Government justifies the central role of the Helmholtz centres with the argument that their specific mission and funding structure enables them to guarantee the sustainable development of the DZG.[161] According to the coalition agreement, the concept of the German Centres for Health Research is to be pursued within a science-led process.[162] Whether the role of the Hemholtz Association will be further strengthened in this process remains to be seen.

Initial experiences with the centres have shown the extent of the development and coordination work required, e.g. in respect of the use of data and proprietary rights, before research projects can be reliably conducted. Since the professional evaluation of the centres is scheduled to begin in 2014, it is not currently possible to assess which of the DZG have successfully negotiated the initial phase, which organisational forms have proven most effective, and whether the overall model can be considered a success.[163] The decision on the future structure and organisation of the centres, as well as the establishment of further centres, will be dependent on the results of the evaluation.

B 1–5 THE FINANCING OF R&D IN THE UNIVERSITY MEDICINE SECTOR

Germany ranked in the middle field for public funding of health-related R&D

The international comparison of state funding for R&D in the health sector is based on data from the OECD (cf. Figure 16).[164] In 2012, health-related R&D in Germany was funded to the tune of EUR 4 billion,[165] equivalent to 0.15 percent of GDP. In the United States and the Netherlands, health-related R&D was funded more intensely (0.23 and 0.20 percent of GDP, respectively). As the corresponding rates for Canada and Switzerland are not available, these countries cannot be included in the analysis. A comparison with further countries shows that state funding for health-related R&D in Germany is in the middle field.[166]

Government funding for health-related R&D (2012) as a percentage of GDP

FIG 16

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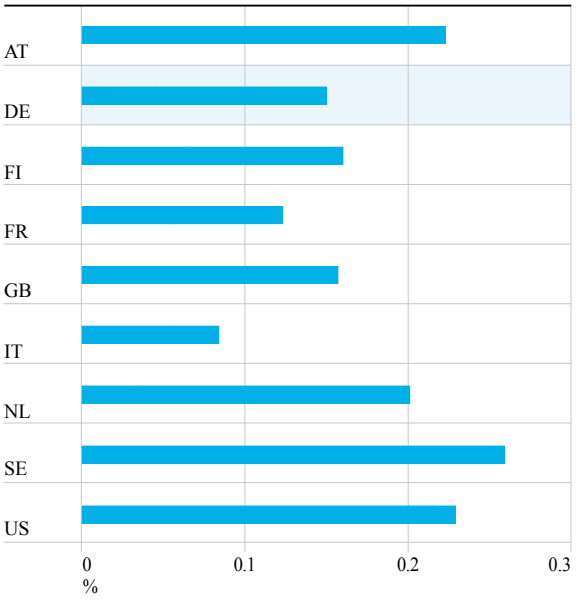


Source: OECD Science, Technology and Industry Scoreboard 2013. Figures on Finland, Great Britain, Italy and Sweden refer to 2011.

Income from healthcare is decisive in determining the budget of German university medicine

The duties of Germany's university medicine sector – consisting of healthcare, research and teaching – are financed from three sources: administrative income (primarily from healthcare provision), basic funds and third-party funding (cf. Figure 17).

- The universities' administrative income is largely composed of revenue from economic activities and assets.[167] In Germany's university hospitals, administrative income from healthcare provision contributes the lion's share to the financing of university medicine. Since 2004, hospitals bill their services according to the integrated, performance-related and flat rate DRG remuneration system (Diagnosis Related Groups remuneration system).[168] Over recent years, the administrative income in the university medicine sector has risen continuously – from EUR 8.8 billion in 2002 to EUR 13.4 billion in 2011.[169] This represents an annual growth rate of 4.8 percent.
- Basic funds in the university medicine sector have increased from EUR 4.3 billion in 2002 to EUR 5.0 billion in 2011.[170] This represents an average annual growth rate of 1.9 percent for this period.
- Third-party funding is composed of revenue raised by the universities in addition to their regular budget. It is almost exclusively used for the financing of research. In 2011, the universities succeeded in raising a total of EUR 1.53 billion in third-party funds in the areas of human medicine and health sciences.[171] Third-party funding has risen continuously at an average rate of 6.6 percent per annum since 2002.

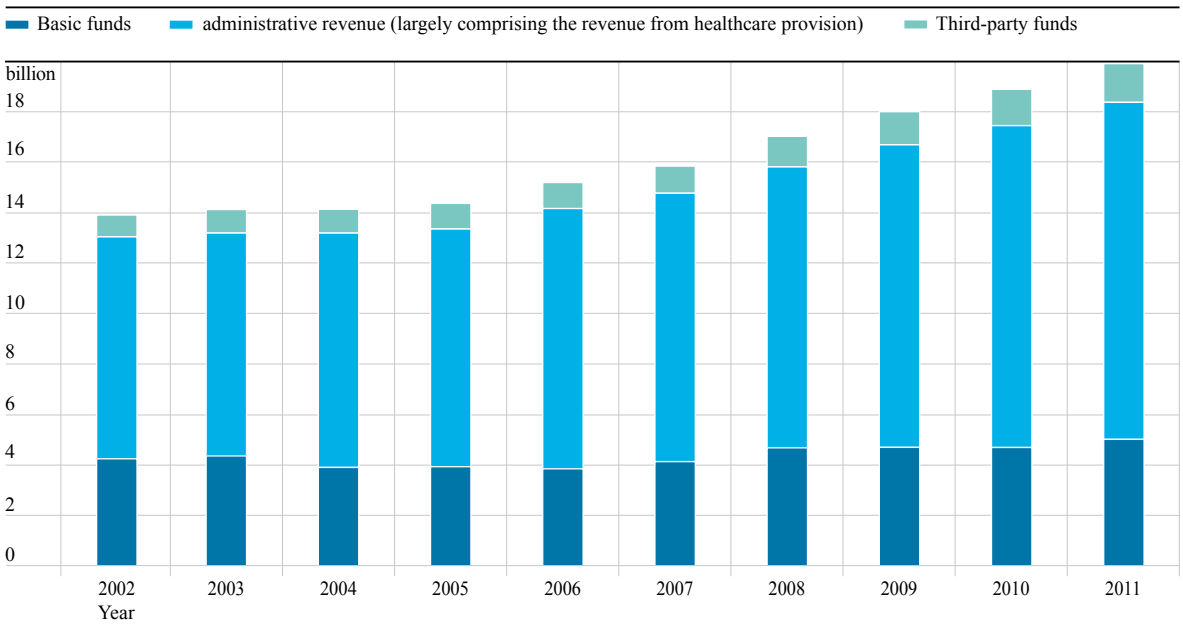
The university medicine budget continues to be largely determined by administrative income. While the percentage of basic funds in the period under consideration fell from 30.6 to 25.3 percent, the percentage of administrative income rose from 63.2 to 67.1 percent.

In 2011, just under EUR 3.45 billion was spent on research and development in the field of medicine/health sciences.[172] That represents 26 percent of the total R&D expenditure at universities (EUR 13.34 billion). Compared with 2002, R&D expenditure in the university medicine sector has risen by 51 percent, i.e. an average of 4.7 percent per annum. This is somewhat higher than the growth in the other fields combined (49 percent, i.e. an average of 4.5 percent per annum).

Basic funds, administrative revenue and third-party funds in university medicine 2002–2011

FIG 17

DATA DOWNLOAD



Source: *Statistisches Bundesamt, Fachserie 11, Reihe 4.5.* Values refer to the human medicine/healthcare sciences subjects group.

University hospitals with systematic additional expenses

Despite the significant increase in income from healthcare provision, a substantial percentage of German university hospitals are faced with funding deficits. In summer 2013 the University Chancellors' Working Group on University Medicine *(Kanzlerarbeitskreis Hochschulmedizin)* predicted that just under half of the university hospitals would have a negative annual result for 2013 and that only 20 percent of the clinics would be in the black.[173] As a consequence, a number of stakeholders, including the Association of University Hospitals in Germany (VUD) and the Medical Faculty Association (MFT) call for financial compensation for the additional costs faced by university hospitals for which the DRG remuneration system does not offer any, or sufficient, financial compensation. It is argued[174] that the university hospitals are subject to above-average financial pressures, e.g. as a result of a relatively high percentage of extreme cost cases that are not adequately covered by the DRG system, insufficient funding of the university outpatient departments, the absence of performance-related and timely financing of new examination and treatment methods as well as a high percentage of physicians undergoing further training.

To the extent that the university medicine sector is faced with unremunerated costs, there is a danger that loss-making healthcare provision in the university hospitals will be subsidised by funds that are actually meant for research and teaching. Thus, in the past cost shifting has been criticised,[175] according to which, as a consequence of poor transparency, there is no guarantee that funds earmarked for research and teaching at the university hospitals are exclusively used for this purpose. Instead, the existing framework conditions and incentives would tend to suggest that loss-making healthcare provision is being subsidised. According to the University Chancellors' Working Group on University Medicine, the "close financial links between clinic and faculty result in the diversion of funds designated for research and teaching to the offsetting of losses from healthcare provision."[176] In the view of the Expert Commission, it is correct that research resources within this context are not always used for their intended purpose.

In other countries, systematic additional expenses faced by the university hospitals resulting from research or training are frequently taken into account – as is the case in Canada, the Netherlands, Switzerland

and the United States.[177] Furthermore, in the US, there is additional remuneration for high cost cases:

- In Canada the provincial health ministries award the Academic Health Science Centres (AHSC) a subsidy for research and training.
- In the Netherlands the university hospitals (UMC) receive additional funding for their special role in research, training and innovation – the so-called "academic component" for research, financed by the ministry of health. The UMC also receive a contribution from the education ministry for training and research.
- In Switzerland hospitals are paid an additional pro-capita flat rate for the further training of physicians. As a matter of principle, these flat rate payments are higher for university clinics; however, they are also awarded to non-university hospitals where training is conducted.
- In the Unites States additional expenses are not compensated for directly. However, hospitals can receive additional operational funding to cover indirect costs resulting from the further training of medical specialists (Indirect Medical Education Index), the direct costs of the training of assistant doctors (Direct Graduate Medical Education) and the treatment of Medicare and Medicaid patients. Furthermore, additional remuneration for high cost cases is also provided. University hospitals benefit from these supplementary financing regulations to a high degree.

The coalition agreement between CDU, CSU and SPD addresses this problem in Germany.[178] Accordingly, remuneration of the special duties of university hospitals and maximum care hospitals within the DRG system is to be improved. The Institute for the Hospital Remuneration System (InEK) has been commissioned to develop a suitable special remuneration system by the end of 2014 for high cost cases that cannot be properly accounted for within the flat rate per case system. Furthermore, the services of the university outpatient departments are to be adequately remunerated in future.

The VUD and the Academic Advisory Board of the German Medical Association estimate the funds required to meet the systematic additional expenses incurred by university hospitals at around EUR 1 billion per annum.[179] The National Association of Statutory Health Insurance Funds *(GKV-Spitzenverband)* refers to the InEK analysis due at the end of 2014, which will indicate where cost deficits as well as cost surpluses have been incurred.[180]

The MFT and VUD are doubtful whether a change to the DRG system alone will be sufficient to completely offset the systematic additional costs incurred by university hospitals at the required speed.[181] Together with the German Society for Internal Medicine (DGIM) and the University Chancellors' Working Group on University Medicine, they see the need to introduce a system subsidy as an independent source of financing for the university medicine sector.[182] In the opinion of the VUD, both the statutory health insurance funds and the BMBF could be considered as potential financiers, as important additional costs have a clear relationship to either healthcare provision or research.[183] In contrast, the German Medical Association considers specific additional payments linked to concrete performance parameters to be superior to flat rate system subsidies.[184] For example, a fictive standard subsidy for research and teaching per student, or a system modeled on other student performance figures and third-party funding procurement would be expedient.

The Expert Commission acknowledges that the university medicine sector is subject to additional expenses for which there is at least partial compensation in all the comparison countries examined, with the exception of Germany. As a result, research at German university hospitals is at a disadvantage relative to comparable institutions abroad. There is also the danger of systematic cross-subsidisation of healthcare provision using research funds.[185] The Expert Commission thus welcomes the fact that the governing parties have addressed the problem of additional expenses in their coalition agreement.

B 1–6 CLINICAL STUDIES

The situation of clinical studies in Germany has improved

Clinical studies play a prominent role in the translation of the results of basic research into patient care. They are compiled with the participation of patients, i.e. test persons. A distinction is to be made between clinical trials and observational studies.[186] In the case of clinical studies, participants receive a specific treatment that is carried out according to a study plan. The goal could be e.g. to test the safety or efficacy of medication or medical devices. In the case of observational studies, no specific (additional) treatment is specified on the part of researchers. Instead, the aim is the systematic collection of data on specific patient or population groups.

Patient-oriented clinical research did not become the focus of medical research in Germany until well into the 1990s.[187] In 2003, the BMBF and the DFG introduced continual funding of clinical studies as part of a joint initiative.[188] In recent years, the BMBF has carried out increased structural funding measures as a complement to project funding with the goal of improving the framework conditions for patient-oriented clinical research in Germany (cf. Box 5). According to existing evaluations of these structural funding measures, they successfully complement the

BMBF structural support measures to improve framework conditions for patient-oriented clinical research[189] BOX 05

- Coordinating Centres for Clinical Trials (KKS):[190] The KKS are designed to support all the processes involved in clinical trials. They play the role of a central service organisation for the universities, providing personnel and logistical resources for the planning, implementation and evaluation of clinical trials. The BMBF financed the creation of twelve KKS between 1999 and 2009 with a total of EUR 38 million. Furthermore, within the framework of the BMBF's public announcement "Coordinating Centres for Clinical Trials", the Pediatric Network for the development and testing of pharmaceuticals for children and young people within the KKS (PAED-Net), the Study Network Surgery (CHIR-Net) and the German Clinical Trials Register (DRKS) have been or will be supported.[191]
- Clinical Study Centres:[192] The Clinical Study Centres are designed to coordinate patient-oriented clinical research at the university hospitals. Furthermore, they are designed to train study personnel and young scientists. In a first round of funding from 2007 to 2011, the BMBF financed Clinical Study Centres at six sites to the tune of around EUR 24 million. Funding will continue in a second round ending in 2015 with EUR 20 million being awarded to five sites. The sites will be equipped with the necessary resources, study know-how will be developed and the recruitment potential of the hospitals, i.e. their regions, will be ascertained.
- Integrated Research and Treatment Centers (IFB):[193] In the period from 2006 to 2015, several centres are being established with the help of IFB funding. Each of the centres will specialise in one important disease area and encompass both research and treatment, and contribute towards strengthening the profile of the respective medical faculties and their university hospitals. The funded universities are to develop suitable, cross-disciplinary structures in order to increase the attractiveness of patient-oriented research and to improve support for young researchers. Up to now eight IFB concepts have been funded to a total of EUR 148 million.
- Competence Networks in Medicine:[194] Since 1999, the BMBF has funded a total of 21 Competence Networks in Medicine covering a range of different diseases. Horizontal networking is designed to facilitate interdisciplinary cooperation between hospitals and basic research; vertical networking is designed to promote the integration of all levels of research and patient care as a means to accelerate knowledge transfer. With the conduction of multi-centric therapy studies within the networks progress in clinical research is to be achieved. In the period between 1999 and 2007 a total of around EUR 225 million was awarded to 17 competence networks. Around EUR 250 million is currently earmarked for the funding of competence networks over a twelve-year period.

project funding of clinical studies through the creation of an infrastructure.

According to the evaluation of the Coordinating Centres for Clinical Trials (KKS) and the Clinical Study Centres, these funding measures have succeeded in establishing structures for patient-oriented clinical research which continue to function after the funding from the BMBF has ended.[195] The structures offer a broad palette of advisory and consultation services, thus functioning as full-service organisations for the planning and implementation of clinical studies. Thus, according to the evaluation, they have assumed an important local role in many clinical trials and have had a positive influence on their quality. Thanks to their training and further training offers, they have had a positive effect extending beyond the centres themselves, improving the competences of participants in respect of the planning and implementation of clinical studies. At many sites, the KKS structures have led to a more professional cooperation between university medicine and the pharmaceutical industry. However, the evaluation also concluded that the funded centres were less successful in achieving the goal of influencing the faculties and clinics in order to bring about changes and improvements in the framework conditions for research. In addition, there were acceptance problems on the part of the clinicians at a number of sites. The financing situation of the centres is problematic: in many cases the institutions have succeeded in procuring more third-party funds following the end of the BMBF funding and a reduced or constant level of financing from federal state funds. However, this was frequently accompanied by a greater focus on studies financed by industry as well as a reduction in the range of services offered.

The evaluation of the Competence Networks in Medicine[196] attributes a strengthening of non-commercial medical research in Germany to the support measures. The competence networks facilitate the recruitment of patient samples of a sufficient size and multicentric approaches for the generation of valid and evidence-based results.[197]

High number of clinical trials in Germany

ClinicalTrials.gov – a service provided by the NIH – has recorded around 156,000 clinical trials worldwide. Around three quarters of these trials were conducted in North America and Europe (cf. Figure 18). A quarter of the ca. 44,000 European trials were conducted with German participation (cf. Figure 19).

According to a survey among experts from industry, academic clinical trial units and clinical research organisations, Germany, Great Britain and the Netherlands are considered the best locations for clinical trials in Europe.[198]

However, there are hardly any international comparative figures for the costs to pharmaceutical companies of conducting clinical trials. A report financed by the NIH published in 2010 states that clinical trials conducted in Germany are only half as expensive as studies conducted in the United States.[199] The comparison countries Canada, the Netherlands and Switzerland were not included in the evaluation. According to an earlier study from Charles River Associates,[200] which provided an international comparison of the average costs per patient for phase III trials, those conducted in Germany were well below those in the United States and Canada and at a similar level to those in the Netherlands.

Adequate structures required for clinical research in the field of rare diseases

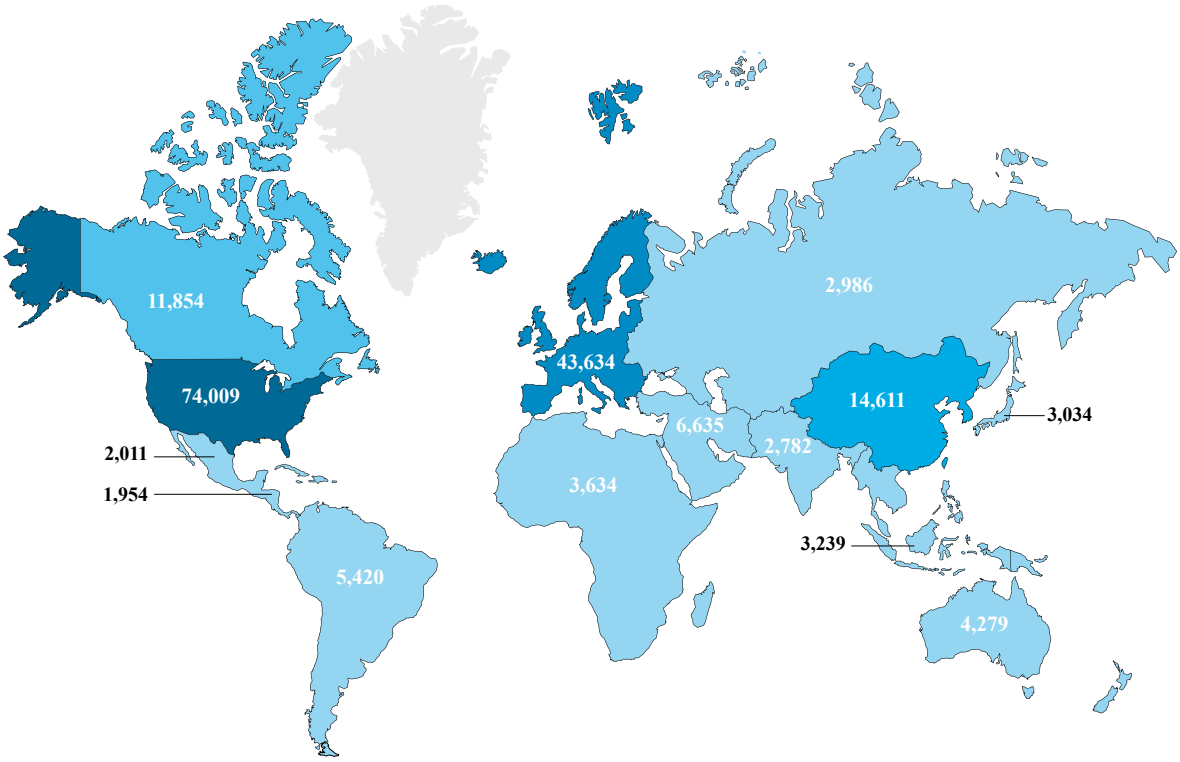
The causes of many rare diseases (RD) (cf. Box 6) have not been investigated yet. Establishing their causes is not only of importance for the treatment of patients with RD; it can also contribute to an understanding of fundamental biomedical relationships and thus of common diseases.[201] The reason for this is that RD can generally be traced back to a few individual factors which can be intensively and extensively researched.

RD healthcare provision and the RD research landscape currently lack adequate structures. Against this background, the BMG and the BMBF, together with the German Alliance of Chronic Rare Diseases (ACHSE) have developed a national action plan for people with rare diseases, which was presented to the general public in August 2013.[202] The national action plan comprises 52 measures designed to assist in the creation of medical care structures, the pooling of competences, and improving research in the field of RD. The aim is to promote cooperative

Number of clinical trials registered worldwide by ClinicalTrials.gov

FIG 18

DATA DOWNLOAD



Source: own depiction based on http://clinicaltrials.gov/ct2/search/map?map=
(last accessed on 10 January 2014).

research and the networking of science and hospitals in a targeted fashion. The national support measures are to be coordinated and supplemented at a European and interdisciplinary level. For the period until 2018 the BMBF has earmarked EUR 27 million of project funding for national and European research cooperation. The Expert Commission welcomes the plan to strengthen cooperative research and the networking of science and hospitals. However, it questions whether the planned measures are sufficient to achieve an adequate pooling of research resources in the area of RD. The question as to whether new organisational forms need to be developed for research into RD also needs to be posed.[203]

The European Union also supports research into RD. For example, within the framework of the 2014 – 2015 support phase of the Horizon 2020 programme, the development of new therapies for RD is being funded, European Reference Networks supported and ERA NET co-financed in the area of RD.[204]

TECHNOLOGY TRANSFER AND COOPERATION WITH THE PRIVATE SECTOR

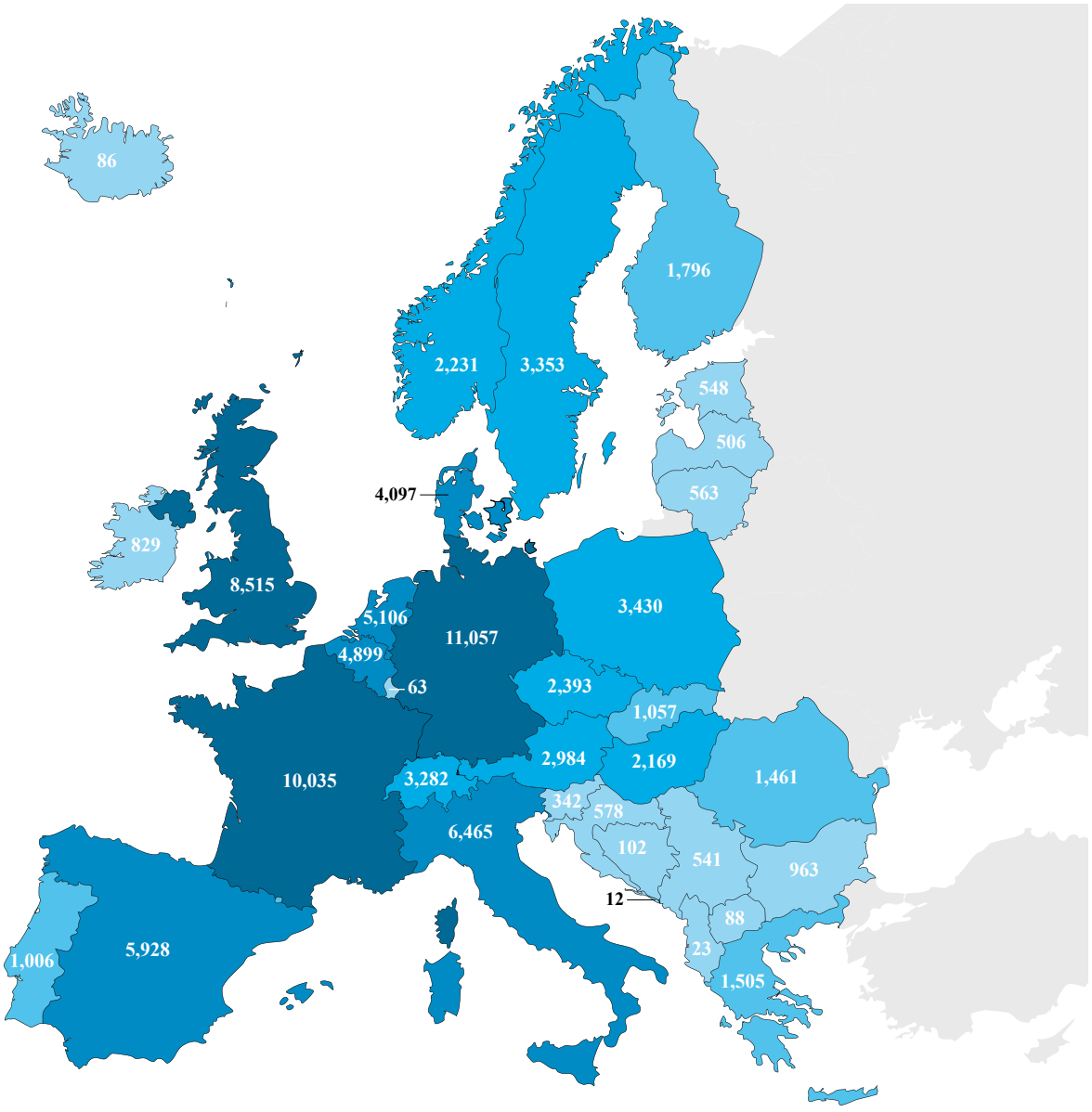
B 1 – 7

Declining relevance of industry as provider of third-party funding

In 2011, around 26 percent of third-party funding received by university medicine was attributable to industry.[205] These funds amounted to approximately EUR 357 million. In recent years, however, the funding level provided by industry has been stagnating, while external funding as a whole experienced an increase. Between 2002 and 2011, the proportional value of third-party funds from industry sources declined from 39 to 26 percent. In the higher education

FIG 19 **Number of clinical trials registered in Europe by ClinicalTrials.gov**

DATA DOWNLOAD



Source: own depiction based on http://clinicaltrials.gov/ct2/search/map?map=EU
(last accessed on 10 January 2014).

BOX 06

Rare diseases (RD)

Diseases are classified as rare when they are contracted by no more than five out of 10,000 people.[206] A total of around four million people in Germany and around 30 million people in Europe suffer from one of the estimated 7,000 to 8,000 rare diseases. RD generally have genetic causes, are seldom curable and frequently manifest themselves in several organ systems simultaneously.
For a long time due to high R&D costs and a relatively small sales market, industry showed little interest in bringing medication against RD – so-called orphan drugs – onto the market. Consequently, both the United States and the EU have taken measures to establish incentives for the development and market entry of orphan drugs.[207]

The field of RD poses special challenges, both with respect to patient care and research:[208]
– RD are frequently diagnosed late or not at all. As several organs are generally affected, as a rule, complex and interdisciplinary diagnostics and treatment is required. The causes of many RD have not been researched yet. Consequently, corresponding therapies are frequently unavailable.
– The integration of basic research and clinical research is of special significance for research into RD. However, difficulties resulting from, on the one side, the low number of researchers working on RD, and on the other, the regional distribution of patients, need to be overcome.

sector as a whole, this proportion declined from 26 to 21 percent in the same period.

Clinical trials as core field of cooperation with private sector

The conduction of clinical trials is a core area of cooperation between the university medicine sector and the pharmaceutical industry. Around 80 percent of clinical trials conducted in Europe are commercially sponsored, mostly by pharmaceutical companies (cf. Table 6). The pharmaceutical industry, in turn, expends well above 50 percent of its R&D budget on clinical research.[209]

Clinical trials frequently lead to debates on the contributions made by companies and public institutions and the reimbursement of the university hospitals' costs.[210] Private enterprises are internationally flexible in their choice of partners and often make use of subsidies for clinical trials offered by some countries. In Germany, the costs of clinical trials were inadequately calculated for a long time. Many of the German university hospitals have only recently established adequate cost accounting systems.

Broadening scope of collaborations with private sector

In addition to clinical trials, at least medium-term cooperation projects with a somewhat broader scope have become increasingly important as a means of cooperation between university medicine and industry in recent years.[211] These projects generally start at a much earlier phase of the research process, often starting in the basic research phase. These projects go further than individual studies and may include a broad range of cooperation forms (cf. Table 7). Large pharmaceutical companies choose their university partners at an international level, with a large number of relevant cooperation projects to be found in the United States and Great Britain in particular.[212]

The general public has occasionally expressed the concern that collaborations between university medicine and private enterprises jeopardise the research freedom and independence of university hospitals.[213] To create public acceptance for such collaborations, they should be designed in a way that safeguards the legitimate interests of the company and prevents conflicts of interest on the part of university medicine.

Room for improvement in the area of patent exploitation

In university medicine, technology transfer, i.e. the transfer of academic research and development results to enterprises for the purpose of economic exploitation, has become more important in recent years.[214] The most prominent modes of technology transfer are patent applications and patent exploitation as well as the creation of spin-off enterprises.[215]

TAB 06 **Clinical trials 2005–2012 according to source of funding**
(figures in percent)

DATA DOWNLOAD

	2005 (28.1.)	**2006** (03.01.)	**2007** (01.01.)	**2008** (01.01.)	**2009** (01.01.)	**2010** (01.01.)	**2011** (31.12.)	**2012** (31.12.)
commercial	89.0	82.0	81.0	80.0	79.5	79.0	79.0	79.0
non-commercial	10.0	17.0	18.5	19.5	20.0	20.5	21.0	20.0

Clinical trials according to source of funding as a percentage of all clinical trials per year. Residual amount not included.
Own depiction based on Loos et al. (2014) based on https://eudract.ema.europa.eu/document.html#statistics (last accessed on 6 June 2013).

TAB 07 **Examples of enhanced research cooperations between university medicine and industry in Germany**

DATA DOWNLOAD

Cooperation	**University medicine partners, and non-university research organisation**	**Industrial partners**	**Year**
Strategic alliance for promoting preclinical research in the field of pulmonary vascular diseases – enhanced cooperation in the area of degenerative lung diseases	University of Giessen	Pfizer	2009 and 2013
Financing of a research group at the CPC and iLBD on research into new cell therapy methods with chronic lung diseases	Comprehensive Pneumology Center (CPC, partners: Helmholtz Zentrum, LMU University Hospital Munich, Asklepios Fachklinik München-Gauting) and Institute of Lung Biology and Diseases of Helmholtz Zentrum München	Roche	2010
Endowment of a chair in the field of gastroenterology	University of Erlangen-Nuremberg	Abbott	2010
Scientific collaboration in the field of stroke research – additional partnership within the framework of a diabetes alliance, also including the joint Sanofi-Charité diabetic laboratory	Charité	Sanofi	2010 and 2012
Creation of the public-private partnership research association Boehringer Ingelheim Ulm University BioCenter (BIU) – focus on research into neurodegenerative, cardiometabolic and pulmonary diseases. Jointly funded by Boehringer Ingelheim, the federal state of Baden-Württemberg and the University of Ulm.	University of Ulm	Boehringer Ingelheim	2011

Source: own depiction based on Loos et al. (2014) using data by vfa; own internet research.[216]

Since 2002, universities in Germany have been able to make use of patent exploitation agencies, which have been established mostly at a federal state level.[217] In some cases, e.g. at the Charité Berlin and the University of Heidelberg, medical faculties have established independent technology transfer agencies.

To promote patent applications, a number of major German universities have established their own patent exploitation agencies, among them Munich and Heidelberg. This means that researchers active in these locations are no longer dependent on the respective federal state's patent exploitation agency, but can turn to local experts who are familiar with the researcher's work and his or her specific needs. However, the creation of independent patent exploitation agencies is not an option for small universities.

The introduction of a grace period would mark a further step in promoting patent applications. Researchers at universities are still faced with the dilemma of having to publish or patent their results as swiftly as possible in order to prevail in scientific competition. Since medical research is a dynamic research area with high patenting activity, patenting barriers are particularly problematic here. In the view of the Expert Commission, this conflict could be partially mitigated through the introduction of a grace period.[218]

Venture capital-backed start-up businesses as important innovators in medical research

In the long term it will be important to foster an entrepreneurial culture at Germany's tertiary education institutions, a culture that continues to be comparatively poorly developed in Germany. In the United States and Canada, for instance, entrepreneurial training is part of the curriculum of scientists and physicians. In contrast to that, physicians in Germany receive only little guidance with regard to starting up a business.[219]

Both new enterprises and universities together considerably contribute to the discovery of innovative drugs and the development of drugs related to new fields of application that have not been considered previously.[220]

The development of drugs often incurs high R&D costs in conjunction with relatively high project risks. Due to this, many new enterprises from the life sciences sector are dependent on large sums of venture capital. Yet, in Germany the financing of capital-intensive early-stage projects continues to be an issue.[221] The Expert Commission has repeatedly called for the necessity to improve conditions for venture capitalists, which continue to be unfavourable to date. In the coalition agreement, the governing parties have agreed to adopt a venture capital law to improve the legal and fiscal framework for venture capital based on different financing options.[222] The Expert Commission expressly welcomes these plans.

USE OF ICT IN MEDICAL RESEARCH B 1–8

Information and communication technologies (ICT) are becoming ever more relevant in medical research.[223] In addition to the creation of networks and the use of large amounts of data – to be further analysed in the following example – a range of other topics are also relevant here. These include hardware and software solutions required for genetic research, the support of workflows and quality management in clinical trials, as well as the IT infrastructure used in biobanks.

ICT opens up networks and research resources

Interdisciplinary cooperation and the efficient use of scarce research resources are continuously gaining relevance in medical research. ICT can supply important tools to promote the networking of scientists and the provision of information on available research resources. Open-source solutions for this field of application include Harvard Catalyst Profiles and eagle-i (see Box 7). In future, medical research institutions should make stronger use of the opportunities offered by ICT for networking and the efficient use of scarce research resources.

Availability and use of large data sets becoming ever more important

The term "big data" refers to the analysis of large amounts of complex data from multiple sources with a high processing speed. In biomedical research, the use of such large data sets is playing an increasingly important role. The smart merging, linking and evaluation of such data sets can open up new prospects for research. Big data could provide German and European locations with the chance to distinguish themselves in medical research. Yet, the use of large data sets is often limited by the fact that necessary data infrastructures are lacking and scientists are insufficiently trained in dealing with big data. Further core challenges include the protection of sensitive patient information as well as the development of methods for securing, aggregating and processing heterogeneous, non-standardised data.

To advance the utilisation of clinical data for research, the open-source solutions i2b2 and SHRINE have been developed in the United States (cf. Box 7). The i2b2 software is characterised by its ability to process highly heterogeneous data from multiple hospital information systems.[224] i2b2 is becoming more and more established also in Germany and Europe.[225] In Germany this software is used e.g. at the university hospitals of Erlangen-Nuremberg, Göttingen and Leipzig.[226] Under the umbrella of TMF (Technology, Methods, and Infrastructure for Networked Medical Research), a networking platform for medical research in Germany and within the framework of a research consortium funded by the BMBF, said institutions are working on making i2b2 more accessible to stakeholders from the German research system.[227] Furthermore, a Europe-wide public-private partnership project that also involves large pharmaceutical companies, is also based on i2b2/SHRINE.[228]

The BMBF provides several measures to support the use of large data sets for biomedical research.[229] However, the Federal Government has not yet presented a concerted strategy for tapping the potential of using large data sets for biomedical research. In contrast to that, the NIH initiative Big Data to Knowledge (BD2K) has been launched in the United States, which aims to train bioinformatic specialists and advance the development of data infrastructure (cf. Box 8).

QUALIFICATIONS AND WORKING CONDITIONS IN MEDICAL RESEARCH B 1–9

Lack of scientific basis in the training of medical students

In recent years, the training of medical students at German universities was increasingly focussed on specialised skills and on strengthening practical medical activities. As practical training elements have been brought to the fore, there are now calls for a stronger scientific focus in the training of medical students. The Association of the Scientific Medical Societies in Germany (AWMF) has pointed out that the current training regulations and their implementation at medical schools pose the risk that "the scientific foundations of medical subjects are not adequately represented in today's academic curriculum."[230]

The practice and patient-oriented design of medical degree courses is often cited as the reason why the interest in clinical research is declining and fewer and fewer medical students opt for an academic career. Furthermore, the lack of scientific quality of doctoral theses in the medical field is another issue that is frequently addressed. In the view of the German Council of Science and Humanities *(Wissenschaftsrat),* medical doctoral theses often have the quality of a graduate thesis and thus fail to meet the standards of independent research work.[231]

The debate on medical training, and especially the question of balancing practical experience with scientific quality and research relevance, is in full swing not only in Germany, but also in its comparison countries (i.e. the Netherlands, Canada, Switzerland, and the United States). The comparison countries seem to be characterised by a two-staged approach to academic training: while the first stage provides scientific foundations for all students, the second, optional stage provides students with the opportunity to timely choose a research focus and to conduct independent research.[232]

In recent years, a number of medical schools in Germany have introduced specific MD/PhD programmes to improve the academic skills of talented young physicians with a strong interest in research. These programmes provide interdisciplinary research-based academic training in the fields of medicine, life sciences and natural sciences.[233] Medical students with

BOX 07

Use of ICT in medical research – the example of Harvard

Harvard Catalyst Profiles[234]
Harvard Catalyst Profiles is a software tool for creating research networks and for mining specific subject-related expertise. The tool also illustrates how each person is connected to others within the comprehensive research community of the Harvard Medical School, the Harvard School of Dental Medicine and the Harvard School of Public Health. Harvard Catalyst Profiles is based on the open-source Profiles Research Networking Software. This software is used by a large number of institutions worldwide.

Eagle-i[235]
Eagle-i is a national platform developed with the aim of reducing the effort of scientists in search of research resources and avoiding the expense of reproducing existing research resources. Eagle-i was developed by a consortium and has been funded by the National Center for Research Resources (NCRR) to the tune of USD 15 million. NCRR is part of the National Institutes of Health (NIH). Eagle-i currently comprises 50,000 different resources, including resources on reagents, organisms and viruses, biological samples, software, protocols, and core laboratories. Eagle-i is also an open-source platform.

Informatics for Integrating Biology and the Bedside (i2b2)[236]
The i2b2 software facilitates the merging of heterogeneous sets of clinical data and enables the evaluation of data within the framework of translational research. With the help of i2b2, patient cohorts can be selected in a user-friendly manner according to a set of inclusion and exclusion criteria. Today, the i2b2 software is used by a variety of institutions in the United States, and also in Europe and Asia.

The i2b2 software originally emerged from the Research Patient Data Repository (RPDR) developed at Massachusetts General Hospital. In 2004 the Massachusetts General Hospital and the Harvard Medical School successfully submitted i2b2 to be awarded an NIH-grant as a National Center for Biomedical Computing (NCBC). Together with six other NCBCs, i2b2 shall serve as a centre of competence and provide the United States with infrastructure necessary for the efficient processing of clinical data.

Shared Health Research Information Network (SHRINE)[237]
Developed at Harvard, the Shared Health Research Information Network (SHRINE) is based on i2b2 and aims to support researchers in compiling information on large groups of well-characterised patients within a network. Available information currently comprises information on standardised demographic indicators, diagnoses, medications, and selected laboratory results. By returning aggregate patient numbers only, SHRINE ensures the protection of privacy and usage rights of the medical data involved.

SHRINE helps researchers in performing the following tasks: generation of new research hypotheses; planning of research that requires large sample sizes; preparation of grant applications that would benefit from pre-identification and/or pre-characterisation of a potential research cohort; identification of potential cohorts for clinical trials; conduction of research in the areas of public health and health services.

Implemented at Harvard University, the SHRINE network is currently used e.g. by the Beth Israel Deaconess Medical Center, the Boston Children's Hospital, the Brigham and Women's Hospital, the Dana-Farber Cancer Institute and the Massachusetts General Hospital. These institutions are now able to retrieve and evaluate the anonymised data of six million patients.

SHRINE is available as an open-source platform. In the United States there are already several SHRINE networks. In addition, a national pilot project is being conducted to analyse comorbidity in the areas of autism and diabetes. A European consortium spanning five countries is currently evaluating the use of i2b2 and SHRINE for clinical trials, medicine safety and other purposes.[238]

BOX 08

THE NIH Big Data to Knowledge (BD2K) initiative[239]

The use of large data sets is often restricted by insufficient data infrastructures and a lack of qualification among scientists in dealing with big data. To address these issues, the NIH launched its Big Data to Knowledge (BD2K) initiative in December 2012. The initiative aims to support the training of young bioinformatic specialists and to advance the development of data infrastructures. The core elements of this initiative are the establishment of new data centres as well as the creation of Centers for Excellence (CfE) which are to be funded by the NIH to the tune of USD 24 million annually. The Centers for Excellence shall provide impetus by bringing together technical and subject-specific knowledge, thereby improving the analytical skills of the interdisciplinary research teams, while also offering information solutions.

an interest in research can obtain a PhD degree in natural sciences either parallel or subsequent to their medical doctorate degree (MD). Yet, the choice of MD/PhD programmes is still very limited in Germany.[240] Students in Germany who aim for a career in university medicine are still well-advised to invest their time in obtaining postdoctoral qualifications rather than pursuing a PhD in natural sciences.[241] It should also be noted that many physicians with an interest in research often choose to start their specialist medical training (e.g. as an internist, pediatrician, or gynaecologist) immediately after the completion of their general medical studies. These specialist training programmes stretch over five to six years. Such specialist qualification is essential for acquiring a senior position in academic clinical medicine. Yet, early stage clinical training is difficult to reconcile with a PhD degree after the completion of medical studies. If, however, a PhD programme is taken up immediately upon completion of medical studies, it will be difficult to combine this with early stage clinical training.

Dual qualification profiles in the form of MD/PhD programmes are much more common in the United States. This ensures that trained medical professionals with a good understanding of scientific methods are available for research, and that medical research can be closely aligned with the requirements of patient care. The translation of research results into patient care is sustainably strengthened by these physician-scientists and through their work in interdisciplinary teams.[242]

The Expert Commission welcomes the introduction of MD/PhD programmes at German medical schools. The creation of an academic research qualification as a supplement to the existing patient-oriented training contributes to improving the translation of results and to advancing differentiation within the German higher education sector.[243]

Unattractive working conditions for young scientists

Besides these qualification-related issues, working conditions for young scientists are also relevant factors for the international competitiveness of German university medicine. Here it is important to distinguish between factors that play a role for all young scientists in Germany – such as the relatively long qualification phase and a high proportion of temporary positions[244] – and those factors that specifically apply to young scientists in university medicine. These include the strong hierarchies at German university hospitals, issues relating to the recognition of research periods for specialist training, and, most notably, difficulties in combining clinical and scientific activities.

German university hospitals are characterised by steep hierarchies: a fairly small, independent professorial top level is met by a large pool of mid-level and low-level employees with mostly temporary contracts.[245] In fact, there is a general complaint that the predefined hierarchical structures are more alive in medical schools than is the case in other faculties. Hierarchies are less pronounced in the United States, which can be attributed not only to cultural reasons, but also to structural ones. For instance, academic staff in the US are less dependent on their senior professors than those working in Germany.[246] Furthermore, specialist training for doctors is more "school-like" than it is in Germany: in the United States, designated specialist doctors pass through the different training stages according to a set schedule. In Germany, the transition from one stage to another has to be negotiated with the professors in

charge. In the United States it is also more common for young scientists to raise their own research funds. Compared with their German colleagues, they are much more independent in their work, but at the same time they are also under stronger competitive pressure.

Another disadvantage for research doctors in Germany is the intransparent system for the recognition of research periods for specialist medical training. Depending on the regional medical association *(Landesärztekammer)* and depending on discipline, recognition regulations can be quite restrictive and at times even ambiguous. In collaboration with the competent regional medical associations, individual university hospitals have developed model curricula to improve the design of training and research activities. However, a comprehensive solution to the problem is currently not in sight.[247]

The difficulty of combining clinical and scientific activities

The so-called triple burden is another phenomenon specific to medical training. While academics at tertiary education institutions are faced with the double burden of research and teaching, academics in medicine are faced with a third burdening factor: patient care. One of the main problems here is the difficulty of combining clinical and scientific activities. Due to cost pressure on the part of the hospitals, medical staff are largely forced into patient care, leaving only little time for research activities.

The German Council of Science and Humanities has pointed out that many university hospitals seem to perceive research as a spare time activity ("off-duty research").[248] Given the burden of clinical work, for aspiring specialist doctors it is difficult to pursue research activities in addition to academic training.[249]

At a number of medical schools, rotation positions are an established instrument used to improve the compatibility of clinical and scientific activities. Research doctors with duties in patient care may be temporarily exempted from their duties to solely work on a scientific project during a given period of time. Rotation positions are promoted both by the DFG via so-called Gerok positions, as well as by the medical faculties themselves. Yet, the number of rotation positions is still very limited.[250] The problem is further intensified by the funding practices of the BMBF and its project management organisation, DLR (cf. page 64).[251]

The problem of reconciling clinical and scientific activities is less pronounced in the United States. Here, the time a physician may allocate to patient care, laboratory work and teaching is clearly regulated.[252] Thanks to this strict regulation, physicians are provided with fixed working hours (protected time) during which they are exempted from clinical duties, enabling them to fully engage in research activities.[253]

In light of the above issues, the Expert Commission has gained the impression that research at German university hospitals is becoming less and less attractive for medical doctors. A lack of incentives and the difficulties of combining patient care and research activities force physicians with an interest in research to restrict their activities or pursue a research career abroad.[254] Yet, it is precisely this combination of clinical and scientific activities that is a prerequisite for the translation of research results – and, ultimately, for medical research and patient care that meets international standards. Given the current circumstances, Germany is running the risk of falling behind in the recruitment of qualified and motivated researchers, while at the same time losing its best talent.

RECOMMENDATIONS B 1–10

Excellent research and the swift and efficient translation of research results into clinical care are dependent on several factors. An international comparison of medical research locations demonstrates that the geographic proximity of interdisciplinary research institutes, hospitals and enterprises is of particularly great importance in addition to the provision of sufficient funding.

Furthermore, excellence in research also requires a certain critical size of university medicine locations and thus a regional concentration of research institutions. In this context the question arises whether Germany's medical research system is overly fragmented with its 33 university hospitals. In the view of the Expert Commission, these considerations are

an argument against the idea of establishing additional locations, unless these locations display extraordinary innovation potential. University hospitals are highly unsuitable as an instrument to ensure appropriate regional representation.

Furthermore, the success of any medical research location depends on the qualification and motivation of its research and patient care staff. Therefore, the key challenge for German medical research lies in creating internationally competitive working conditions for talented scientists and medical staff within a top-class research area.

Strengthening innovative and interdisciplinary approaches

The Expert Commission welcomes the launch of German Centres for Health Research (DZG) as a means of bundling medical research more effectively. As these centres have been established only recently, little is known about the best organisational forms. Decisions on the founding and institutional design of additional DZG centres should therefore be only taken after the existing centres have been evaluated.

Interdisciplinarity and translation should be promoted through the development of scientific collaborations based on partnerships e.g. between universities and non-university research institutions. Funding incentives and experimental clauses could support the development and implementation of new, strong academic profiles in the area of medical research.

Solid funding basis needed for R&D in university medicine

The bearing of the university hospitals' systemic additional expenses should be balanced out. As these expenses can be partially allocated to patient care and partially to research and training, it is disproportionate to burden solely the health insurance companies. However, great care should be applied when creating a balancing mechanism, as the creation of disincentives generally leads to high costs and is not easily corrected. Therefore, political stakeholders should carefully consider the tools to be introduced for balancing out the additional expenses of university hospitals.

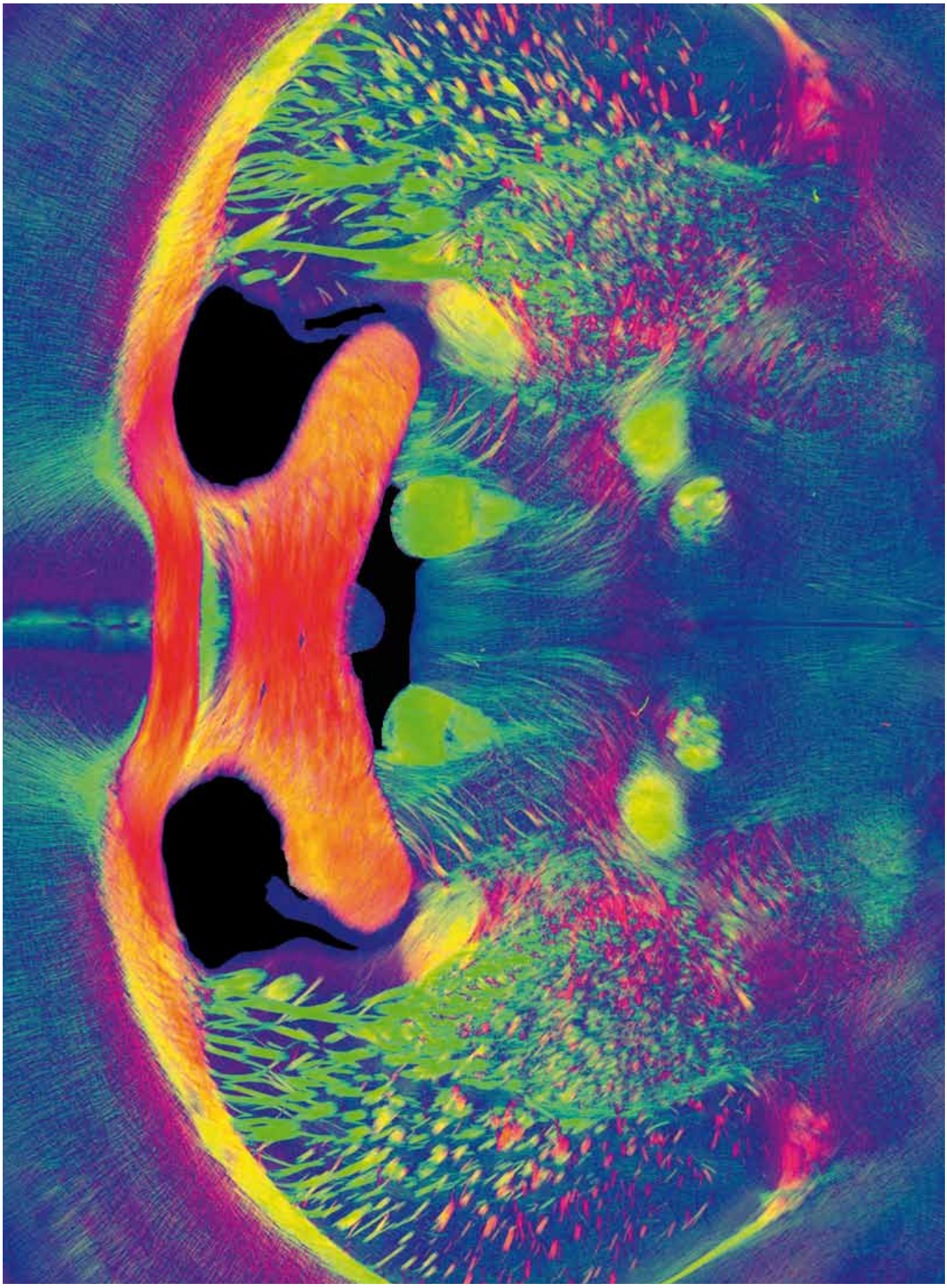
Basic funding for further developing research and teaching should be strengthened not only within the overall higher education sector, but also within medical schools. This should also be facilitated by re-enabling the Federal Government to fund tertiary education institution at an institutional level (cf. the Expert Commission's comments on Article 91b of the German constitution in Chapter A 1). In addition, DFG and BMBF should raise their programme and project allowances within a short time. In the medium term, contracting authorities should introduce a refund of full cost (cf. Chapter A 1). When commissioned with public and private R&D projects, tertiary education institutions must be enabled to charge for the full costs of the project.

Against the background of rising costs and competitive pressure, the Expert Commission recommends concentrating the allocation of research funds for university medicine even further on those locations in Germany that are particularly strong in performance.

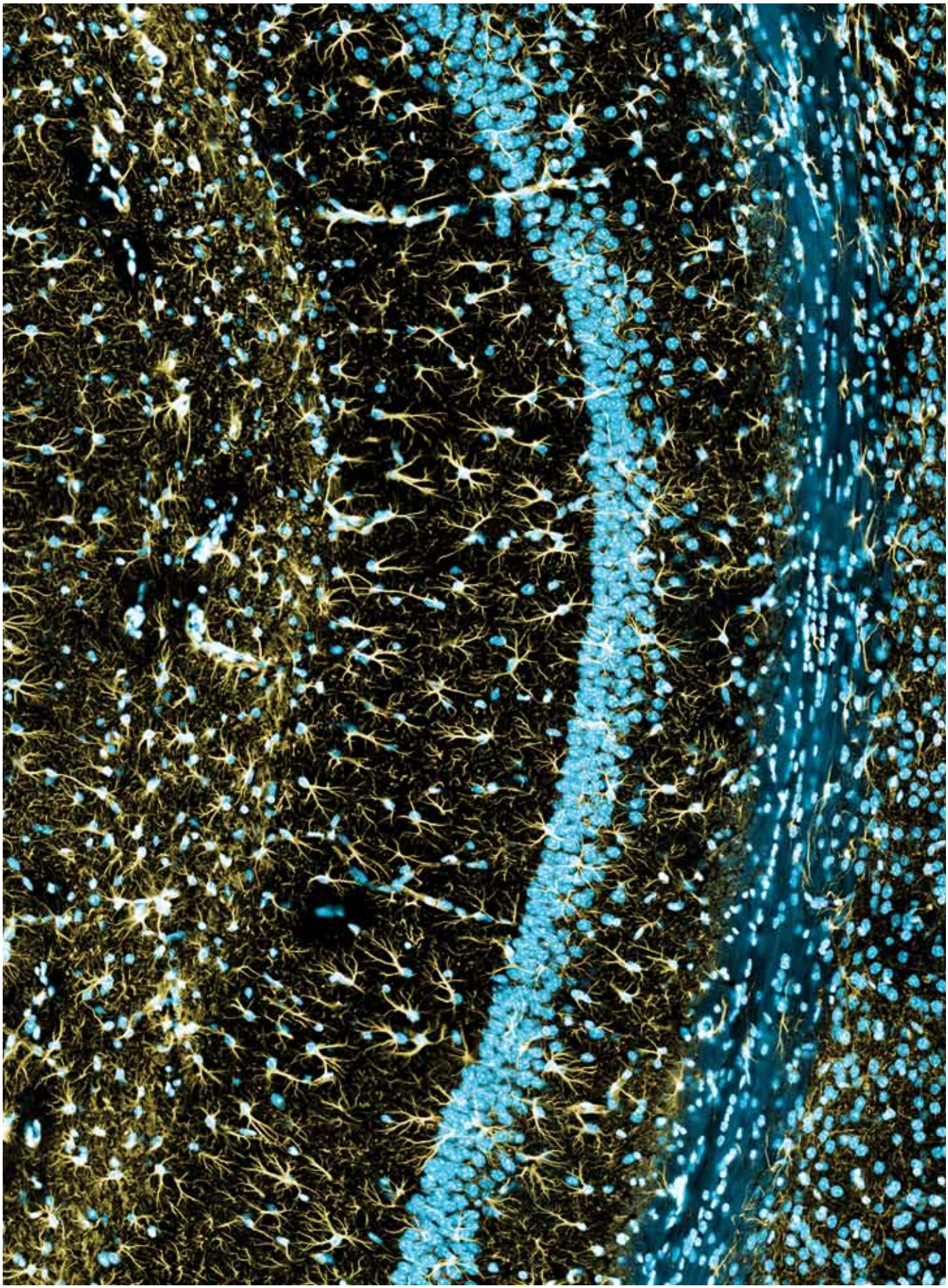
Further strengthening clinical research

The close integration of basic research and clinical research is to be further strengthened. Efforts should be made to promote the geographic concentration of basic research, clinical research and patient care, as well as other stakeholders from the health sector, such as non-university research institutions and businesses.

Centres established in the context of the BMBF structural support measures to improve the framework conditions for patient-oriented clinical research – such as the Coordination Centres for Clinical Trials (KKS) and the Clinical Study Centres – should be developed further according to demand. The relevant establishments should not enter into a publicly subsidised price competition, but should secure a high quality in all clinical trials conducted. Financial self-sustainability must not be the sole success criterion of these centres.



Nerve fibres of the brain in 70 microns thick, histological frontal sections, visualised with Polarised Light Imaging. Here: fibre flow of a mouse.



Hippocampal and neocortical subregions with fluorescent cell nuclei (blue) and glial cells (yellow)

Setting incentives for corporate collaborations and technology transfer

An ongoing professionalisation of tertiary education institutions in the areas of industrial cooperation, cost accounting and intellectual property exploitation could create incentives for enhanced cooperation between medical schools and private enterprises.

A uniform code of conduct for all university medicine locations could help avoid conflicts of interest within corporate collaborations, while ensuring the highest possible level of transparency – even without mandatory disclosure of cooperation details.

A grace period should be introduced in the European patent systems. Researchers at universities are still faced with the dilemma of having to publish or patent their research results as swiftly as possible to prevail in scientific competition. This problem could be partially mitigated by introducing a grace period in the German patent system. Since medical research is a dynamic research area with high patenting activity, patenting barriers are particularly problematic in this regard.

Since venture capital-based start-ups are important innovators in medical research, improving financing conditions for business start-ups is also an important step towards increasing the competitiveness of German medical research. In previous reports, the Expert Commission has already outlined the components of internationally competitive framework conditions for investors.[255] In the training of medical researchers, topics relating to entrepreneurship should be addressed to a much greater extent than previously.

Tapping innovation potential through the use of ICT

University medicine sites and non-university research organisations active in the field of medical research should make intensive use of the opportunities offered by ICT to facilitate networking and the efficient use of scarce research resources. The Expert Commission is very concerned about the fact that Germany's shortcomings in the field of ICT are hampering medical research. The Federal and Länder governments should develop an action plan for the use of large sets of complex data in medical research. In the view of the Expert Commission, this action plan should be integrated into the Federal Government's Digital Agenda (cf. Chapter B 3).

The handling of big data in medicine also calls for an active, solution-oriented debate on data protection issues in order to facilitate the inter-institutional use of patient data for research purposes, while also ensuring sufficient protection of the patients' privacy. Procedures for the anonymised use of patient data should be applied for the purpose of releasing innovation potential without compromising privacy.

Strengthening the scientific components of medical studies

As a general rule, it would make sense to subdivide medical careers into two pathways, one with a scientific focus, and one with a focus on the medical profession.

Tertiary education students with an interest in research must be given the chance to specialise in research topics at an early stage. MD/PhD degree programmes should be expanded further in Germany.

Research careers in university medicine need to be more attractive

In Germany, a career in medical research is less attractive than in other countries. Against this background, German medical research is at risk of losing more and more talented young professionals and of decreasing research quality. A lack of incentives and the difficulties in combining patient care and research activities are the main reasons for these shortcomings.

In order to reconcile research and patient care to a greater extent, German university hospitals should follow successful international examples and introduce additional rotation positions. The Expert Commission recommends introducing fixed time frames (protected time) for research. In the view of the Expert Commission, young scientists are indeed left with too little time for their own research.

General reforms are also needed in the specialist training programmes for doctors, which currently entail

a high degree of uncertainty for physicians active in research. The specialist training phase should be clearly structured and predictable, as is the case in the United States. The creation of transparent recognition regulations for research periods during specialist training would be a step in the right direction. Regulations should uniformly apply to all of the federal states. Depending on the competent regional medical association *(Landesärztekammer)* and depending on discipline, regulations still vary today and continue to be ambiguous at times.

To attract young talented physicians to research, German universities need to offer more favourable career prospects. Research careers are less predictable at German universities, and youngresearchers are highly dependent on their supervising professors. It is often the case that this dependency does not provide sufficient leeway for independent research. New funding and scholarship programmes should be introduced, and existing programmes such as the Emmy Noether programme should be expanded to create room for young physicians with an interest in research.

Improvements are also needed with regard to the financing of research projects. The funding practice of the project management organisation DLR, which operates on behalf of the BMBF, is considered as bureaucratic and unattractive when compared with that of the DFG. Therefore, funding practices should be handled more flexibly.

The remuneration of physicians active in research should be brought more in line with the level of remuneration received by physicians engaged in healthcare activities. The current pay gap reduces the attractiveness of careers in medical research at universities.[256]