Digital Research Reports

Precision Medicine, An International Perspective

An analysis of precision medicine research focused on Russia and Germany

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Foreword

We are happy to introduce this report, dedicated to the Russia-Germany Science Dialogue event coupled with 120 years celebration of Merck's presence in the Russian Federation. This report is based on *Dimensions* data from event partner Digital Science and the following analysis is the fruit of collaboration amongst researchers and authors from Germany, Russia, France, and the United Kingdom. The overarching topic of the report "Precision medicine: Building bridges between health research and medical care", which we have selected, perfectly reflects the discussions at the round table and our dedication to explore, exploit, and reinforce joint efforts in science, innovation, and healthcare, benefiting our communities.

"The overarching topic of this report perfectly reflects our dedication to explore, exploit, and reinforce joint efforts in science, innovation, and healthcare, benefiting our communities"

In this report, we examine the topic of precision medicine as a proxy for the rise of Digital Medicine in recent years. We examine a variety of perspectives and geographic distributions going beyond publications to funding patterns, patent affiliations, and clinical trials – all that makes healthcare research and healthcare innovation grow from idea to application.

When Russia and Germany announced the joint programme of 2019-2020: Two Years of Science, it corresponded with an important milestone in Merck Group history – 350 years of Merck as well as 120 years of Merck presence in Russia. We believe that true innovation and Noble Prize level research rests on global, international collaborations. Scientific and technological breakthroughs find their home in exchanges between science foundations, laboratories, universities, science centres, and innovation and entrepreneurial hubs. We would like to reinforce the exploration of new research trends and inform unique research strategies by opening a discussion on how the global research landscape is transformed into country-level achievements, and on to university-level excellence founded by individual researchers whose work is benefiting society.

Healthcare research collaboration is leading the way to positive impacts on society and we hope that cultural, scientific and social partnerships celebrated during the Two Years of Science dialogue will reinforce existing relationships between Russia and Germany and will build new bridges.

Juergen Koenig, CEO and President, Merck Russia & CIS
Dr. Igor Osipov, CEO, Digital Science Russia & CIS

Introduction

"Precision medicine is not only about identifying and tailoring the correct drugs for a given patient, but is a key central theme"

Over the last 20 years the terms "Precision Medicine" and "Personalised Medicine" have come into general use both inside and outside the medical community. The two terms are now used fairly interchangeably and have become something of a catch-all to describe any medical technique that is customised to the characteristics of an individual patient.

Medicine has, since the beginning of the profession, sought to find ways to improve the lot of those suffering from distress and disease. Until the end of the last millennium, medical approaches can be thought of as being a comparatively blunt tool in the context of modern methods. Precision medicine is not only about identifying and tailoring the correct drugs for a given patient, but it is a key central theme.

Prior to the development of precision medicine, drugs were prescribed essentially on a statistical basis. By that we mean that drugs were broadly tested on representative cohorts of subjects in clinical trials before being brought to market. These studies allowed doctors to understand the chances that any particular drug might be effective on any particular patient in a statistical way. That still left open a significant probability that a patient might receive a drug that was not only sub-optimal for their condition but that instead it may be completely neutral (giving the patient a false sense of security) or even harmful. There are well-known issues with most drugs and how well or how badly they work for patients from different backgrounds. There are also well-studied issues with clinical trials themselves and ensuring that cohorts are representative of the general populous[1].

When a doctor prescribes you a drug today it is almost certainly done without checking your genome to see if a specific drug is a good "fit" for you, family history and personal characteristics. However, in the not-too-distant future, it will be completely usual to perform your genetic profile, store it, and use it to inform the treatment and therapeutic choices that your physician is able to recommend to you. There are many strong drivers to adopt this approach: Although a genetic profile is expensive, the cost is reducing all the time and this typically needs only to be done one time. Once one is in possession of a genetic map for an individual you can use this in perpetuity to assess which drugs will actually have the desired effect, which will have no effect, and which may have damaging side effects – based on these advances in research not only in drug discovery and efficacy but also in gene targeting, therapeutics and resistance mechanisms, prescribing pesonalised drugs will lead to an individual with better health prospects who is happier and with less need for ongoing medical treatment, together with lower incidence of deterioration.

"In the not-too-distant future, it will be completely usual to perform your genetic profile, store it, and use it to inform the treatment and therapeutic choices"

In today's culture, we are used to personalised experiences and we are sold them at every turn. A personalised experience is not just for the wealthy, it is an integral part of our technology-driven life and has become central to the success of everything from social networks and dating websites; from product placement during our browsing experience to content recommendations on any one of a plethora of different platforms such as Netflix. But personalised or precision medicine promises much more than finding the right film or food. It is, in some sense, the ultimate personalised experience. A chance to stay younger for longer, live longer and experience fewer or shorter times of disease during our lives.

"The potential for precision medicine is vast with the opportunity valued not just in the tens of billions but in the hundreds of billions of US dollars[2]"

The potential for precision medicine is vast with the opportunity valued not just in the tens of billions but in the hundreds of billions of US dollars[2]. Yet the technologies being developed and deployed to support this emergent industry are relatively young, having been the result of fundamental research carried out in the last 60 years. As with so many of the other technologies that we benefit from today, the fundamental research has its roots in the 1950s with the dual paths of the work of Watson and Crick around DNA combined with the progenitors of the microcomputer revolution. Ultimately, these foundations lead to developments in genetics and genomic sequencing[3], stem cell biology, nanotechnology and artificial intelligence, all of which play a critical role in the ongoing development of precision medicine.

This report provides a brief overview of the area of personalised and precision medicine since the turn of the millennium, highlighting key areas of development in publication activity. It has been produced in celebration of the Russian-German Science Dialogue and in combination with Merck's 120th Anniversary in Russia. As a result, we pay particular attention to these countries.

Analysis

Digital Science's *Dimensions* database can be used to search the full text of more than 65 million publications together with a further 30 million metadata records; abstracts of 4.4million awarded grants from more than 300 funders; details of more than 38 million patents; and more than 450,000 clinical trials and 400,000 policy documents. All of these records are characterised by having unique identifiers that are mapped to data dictionaries for an enhanced discovery and faceting experience. The database is centred around English-language publications but does include works in other languages. These works are machine translated to facilitate single-language searches. At the time of writing Russian language works are being included in the Dimensions index but do not appear in the analysis below.

We define the area of Precision Medicine by the search string:

"Precision medicine" OR ("Personalised Medicine" OR "Personalized Medicine")

[1] *https://www.scientificamerican.com/article/clinical-trials-have-far-too-little-racial-and-ethnic-diversity/*

[2] *https://www.thejournalofprecisionmedicine.com/global-precision-medicine-market-to-approach-us-172-95-billion-by-the-end-of-2024/*

[3] *International Human Genome Sequencing Consortium, (2001). Initial sequencing and analysis of the human genome, Nature, 409, 860-921, https://doi.org/10.1038/35057062*

Global Landscape

Research into precision medicine around the world has been developing since the turn of the millennium. In the year 2000, just 50 articles were published which used the terms "precision medicine" or "personalised medicine". In 2018, the number of articles published with either term was in excess of 32,000. This rapid rise has meant that there are now more than 170,000 articles that refer to this topic.

Figure 1: Global distribution of research output in Precision Medicine in 2018.

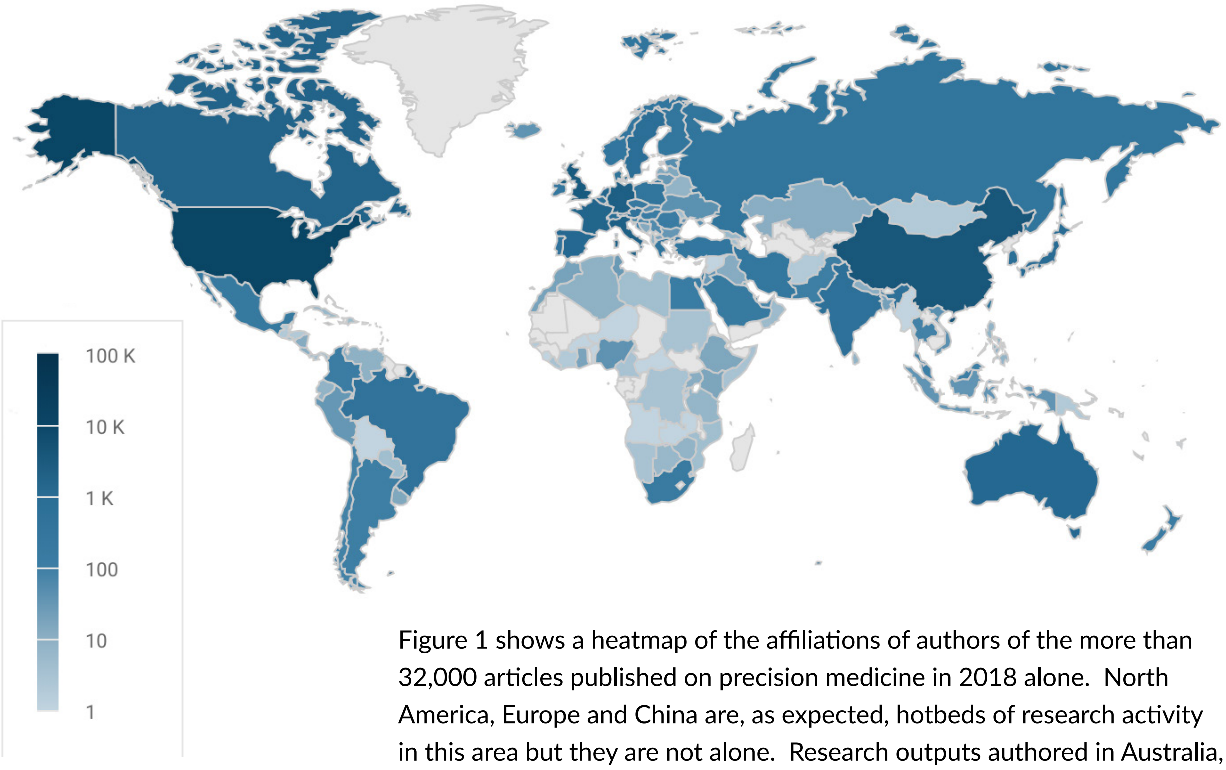


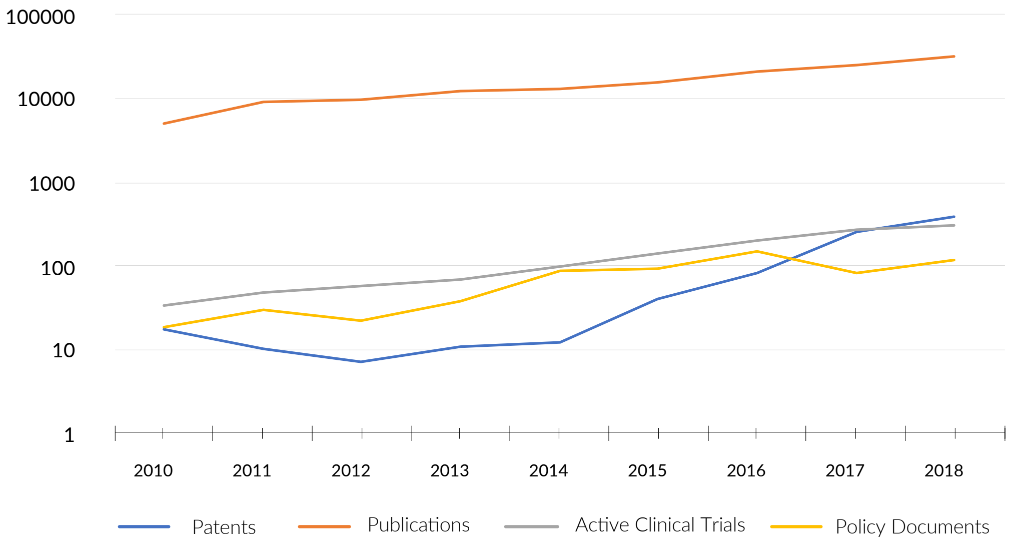
Figure 1 shows a heatmap of the affiliations of authors of the more than 32,000 articles published on precision medicine in 2018 alone. North America, Europe and China are, as expected, hotbeds of research activity in this area but they are not alone. Research outputs authored in Australia, Brazil, South Africa, India and Russia all show the result of significant investment in the field.

As the application of precision medicine in medical practice becomes a reality, the rate of awarding grants has also significantly increased. In 2000, just 14 grant applications (tracked in the *Dimensions* database) were awarded that mentioned precision medicine. The number of grants awarded in 2018 alone reached 654 and totalled more than 160m EUR of funding. Subject categorisation of grants ranged from Genetics (123 awards) to Oncology and Carcinogenesis (110 awards), through Artificial Intelligence (63 awards) to Macromolecular and Materials Chemistry (11 awards). Precision medicine is a rich and diverse field that is beginning to leverage capabilities from across the research spectrum.

"In 2000, just 14 grant applications were awarded that mentioned precision medicine. The number of grants awarded in 2018 alone reached 654"

As with any applied field of research relating to medicine, it is not just the funding and publication activity that is needed in order to show progress but also the patent, clinical trial and policy landscape that is essential to formulate a full picture. In the early stages of development of a field, it is obviously challenging to lodge patents as ideas are still young and their application is unclear. Although the first signals of research publication in precision medicine date from 2000, patenting activity has been relatively low until much more recently, reaching 396 patent applications in the *Dimensions* database in 2018. Patenting activity is now growing rapidly. Clinical trial activity is also at a lower level than publication activity, however, growth in clinical trials is correlated with around 100 new trials starting every year around the globe. The most lagging indicator of any research area is often the effect that it has on policy. With this in mind, it is impressive that there has been a steady stream of policy documentation published since 2000, when there was just a single document regarding human genome research from the UK parliament. Today, there is a vibrant policy environment surrounding precision medicine with around 100 policy documents being published each year in all major jurisdictions. Figure 2 gives a brief overview of the development of these different signals compared with rate of publication.

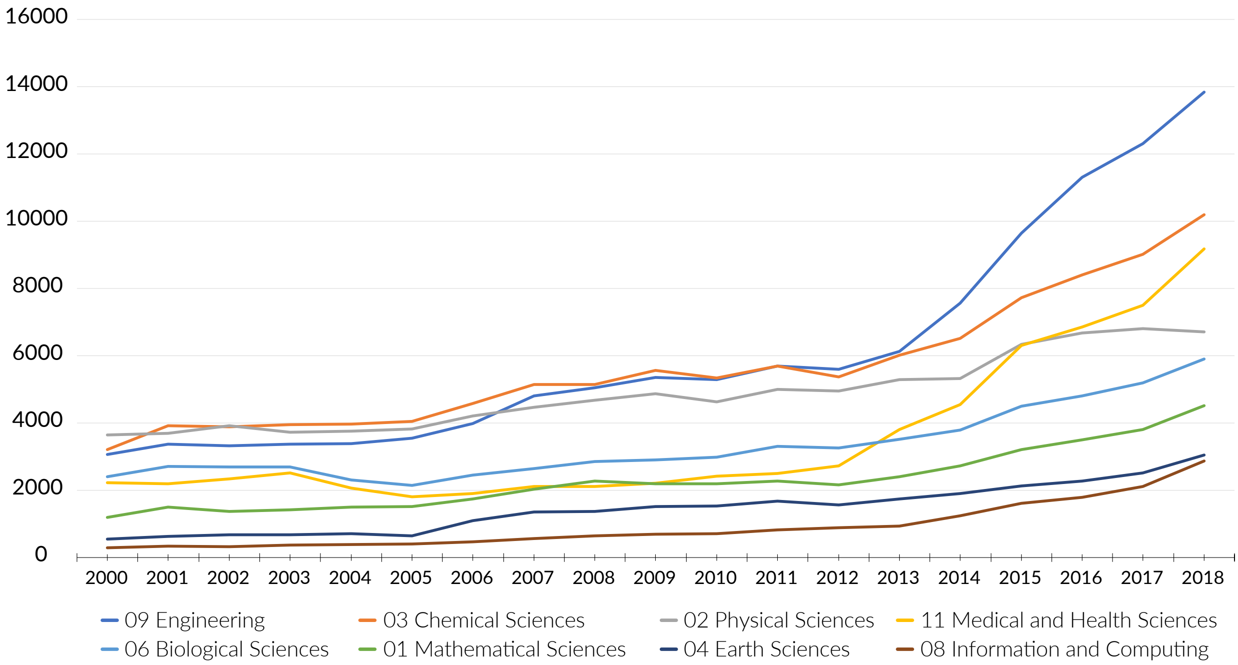
Figure 2: Progression of Patents, Publications, Active Clinical Trials and Policy Documents from Dimensions that mention Precision Medicine or Personalised Medicine from 2010 to 2018. Logarithmic Scale.



The Picture in Russia and Germany

The Russian research system is coming of age, having developed significantly since the turn of the millennium. As is often the case with young research systems, the research institutions are still developing their areas of specialism, and researchers and infrastructure are emergent. As we see in Figure 3, the volume of research in Medical and Health Sciences, has begun to increase significantly since 2012, while Russia's reputation for Engineering is clearly well-deserved.

Figure 3: Publication volumes for Russia by 2-digit Field of Research code.



In 2018, Germany produced an amount of research in Personalised Medicine, as defined by the query above, equal to 5.3% of its overall output, classified principally in the Field of Research code for Medical and Health Science. Since Russia's research system is still, as noted, in its emergent phase, it is impressive that by the same metric, precision medicine is at 3.3%.

Figure 4 shows the top precision-medicine-producing research institutions in Germany in recent years. Each year header has underneath the average number of citations to a precision medicine article from Germany in each year shown. It is noteworthy that the volume of publications is limited and consequently there is a greater level of movement in the order than there would be in the study of a larger field. Despite these drawbacks, we observe that Germany has a cluster of consistently performing institutions in precision medicine research with Ludwig Maximilian University, Charité University Medical Centre in Berlin, the German Cancer Research Centre, TU Munich and the University of Heidelberg all performing consistently at the top of Germany's research output in the field.

Figure 4: Top 12 Research Institutions in Germany by publication volume in 2014, 2016 and 2018. Under each year heading, the average number of citations in 2019 to works in precision medicine produced in that year in Germany is displayed.

The centrality of these institutions in German precision medicine research is also evident from the other metrics that are shown in figure 4: For each institution, the left number (e.g. 80.3 in the case of Ludwig Maximillian 2014) shows the number of citations to the mean average research article published by that institution in the year in question. This number can be compared with the number under the year header in each column (e.g. 35.5 in 2014). The right number (e.g. 13.2% in the case of Lugwig Maximillian 2014) shows the percentage of citations to articles published with at least one Germany-based participant that are associated with papers with at least one institutional participant. We can interpret the left number as a measure of attention associated with the work in an absolute sense, while the right number gives us a measure of the proportion of the attention given to German precision medicine research that has been attracted by the works affiliated with the institution. From these numbers, we see that while Charité University of Medicine Berlin consistently produces the largest amount of work, the attention that work gets both on average and as a proportion of the overall German average is a little lower. On the other hand, Ludwig Maximilian University's research from 2014 clearly had an extraordinary performance, which has been hard to match in more recent years.

It appears to be typical that top German institutions attract in the region of 5-10% of the available attention given to German-affiliated outputs. A final note on the German part of this analysis is that the Max Planck Institutes are treated separately rather than as a conglomerated body. As a result, the Max Planck organisation does not appear in the analysis.

Figure 5 allows us to make a similar exploration of precision medicine in Russia. Russia's research system does not yet have the scale of the German system and hence the ratios in Figure 4 and Figure 5 have been chosen specifically to allow some level of comparison to be made.

"The Russian research system is coming of age, having developed significantly since the turn of the millennium"

Of immediate note is the dominance of the Russian Academy of Sciences (RAS) in all years – both the average number of citations to Russian Academic affiliated works and the percentage of Russian-targeted citations are extremely high for the RAS, given that this is a collective affiliation of many institutions which are part of the RAS family. Nevertheless, there are several impressive individual institute performances with Moscow State University consistently performing in the upper echelons of research in Russian precision medicine. From the Russian table it is clear that the relatively lower volume of publications compared with Germany gives slightly more motion in the lower part of the ordering. However, it is also clear that this is an active field with many institutions taking a role in understanding a field that is still coming of age.

Using the Health Research Classification System (HRCS) gives us another way to compare the output of different countries and entities. HRCS was developed in the UK and classifies research in broad fields[4]. Figure 6 shows the different balances of research exhibited in Russia and Germany, as research nations and systems, and in Merck as a commercial pharmaceutical research organisation. Publication volumes were limited in some cases, so ratios were used to ensure that valid

[4] https://hrcsonline.net/

Figure 5: Top 12 Research Institutions in Russia by publication volume in each of 2014, 2016 and 2018. Under each year heading, the average number of citations in 2019 to works in precision medicine produced in that year in Russia is displayed.

comparisons can be made. It is also important to understand that as a commercial organisation the level of external research publication that Merck is able to support will only show a small indication of their interests and the scale of their research efforts.

From Figure 6, we see that in all cases there is the same dominant subfield/topic around which works in the area of precision medicine cluster: Cancer. In all cases generic health comes second. However, country research strategies decouple from commercial research strategies once we pass the second most important topic. Whereas Germany and Russia are well aligned both in approximate proportion of research and approximate order of importance for the top 6 areas of their research interest, Merck has chosen to focus on different issues, specifically, leaving Cardiovascular and Neurological research in favour of Musculoskeletal and Reproductive research.

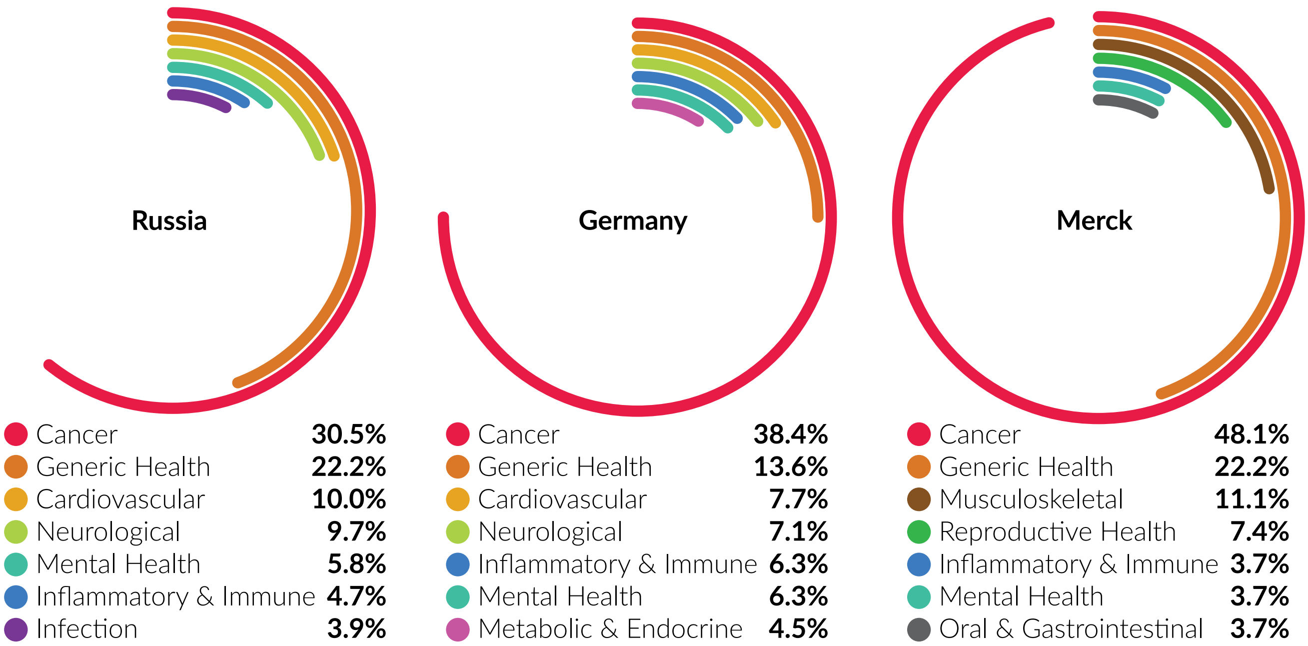


Figure 6: Proportion of precision medicine papers produced by HRCS category for Russia, Germany and Merck. A full circle would represent 50% of research being classified under that topic. Top 7 research areas only shown.

Discussion

Precision medicine is a diverse field that is coming of age. Its development parallels Russia's own development in the clinical and life sciences, both of which can date their significant investment and development to the new millennium. Precision medicine is now showing development not only in publications but also in indicators that signal greater maturity of a medicine subject – patents, clinical trials and policy. Russia, while less developed in some of these measures, shows that it is making similar choices to Germany in the focus for research in this area, which is a good benchmark given Germany's long history as a research nation. It is interesting that Merck, in contradistinction to both countries, takes a different approach to its published research focus. However, this is a healthy difference since Merck will be balancing commercial demands with curiosity-driven research.

While country-level characteristics can be similar, it is critical for the health of the global research landscape that there should be plurality of vision and structural diversity. In the microcosm of precision medicine that we've briefly explored here, it is clear that there are differences of approach between countries and especially with the approach taken by an industrial player in Merck. These differences should be celebrated, especially in the context of the German-Russian Science Dialogue as well as on the anniversary of Merck's 120th year in Russia. The diversity shown here makes for stronger research and ensures greater opportunities for collaboration in the future.

"It is critical for the health of the global research landscape that there should be plurality of vision and structural diversity. In the microcosm of precision medicine"

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