Funding of rare disease research in Germany: a pilot study

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Abstract Collectively, rare diseases are of major public health impact, but research on rare diseases poses major challenges. There are many deterrents for researchers to initiate rare disease projects and for funding agencies to grant support. It can be expected that rare disease research is underfunded, but no systematic assessments on rare disease funding practices were found in the literature. The recipients of grants for rare disease research were identified through the research reports of four German medical faculties, and data on external funding of individual projects were obtained through questionnaires and database mining. Response rates to questionnaires were unsatisfactory. The analysis was thus concentrated on a single faculty, Hannover Medical School, for which 100% data ascertainment was obtained. External funding for rare disease research at this faculty comprises 5.8% of all external research funding in 2006, and 3.8% in 2007. As the first study of this kind, this survey indicates enormous deficits and inequities in rare disease research.

Background

Research on rare diseases poses major challenges. Some 6–8% of the population in developed countries are

believed to be affected by one of the estimated 6,000 different rare diseases, each affecting, by definition, fewer than 1 in 2,000 people (EURORDIS website, www.eurordis.org/IMG/pdf/princeps_document-EN.pdf), but collectively constituting a major public health impact. Due to the “epidemiological transition,” rare diseases are gaining importance for community genetic services also in emerging economies. Ongoing research projects on rare diseases often fulfil direct service functions as they may provide genetic tests not available in routine laboratories. The Orphanet database of rare diseases (Orphanet website, www.orpha.net) has collected, as of January 2011, prevalence data on 560 rare conditions, the cumulative prevalence of which amounts to 4.7% (www.orpha.net/orphacom/cahiers/docs/GB/Prevalence_of_rare_diseases_by_decreasing_prevalence_or_cases.pdf). Thus, most rare conditions are so infrequent that, if being recognised as a research target at all, patient recruitment is difficult. The oftentimes necessary formation of local, national, or international research networks; the difficulties in convincing granting bodies about the relevance of funding; and the perceived greater public health impact of research on common diseases are likely deterrents for researchers to undertake rare disease projects. These considerations lead us to expect that rare disease research is underfunded and that action plans are needed to improve this situation, but we could not find in the scientific literature any systematic assessments on rare disease funding practices that would support or refute our expectation. We therefore conducted such a study in Germany between 2005 and 2007. We regard this as a pilot study, and we hope that it will elicit further attempts in other European countries and thereby support joint activities in rare disease research.

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Methods

Various methodological approaches to study research funding are conceivable. Some of the large granting agencies, such as the Deutsche Forschungsgemeinschaft, maintain and publish databases of all funded projects, and such databases could in principle be interrogated specifically for rare disease projects. However, databases including that of the Deutsche Forschungsgemeinschaft (DFG-GEPRIS website, www.dfg.de/gepris/) are not designed to facilitate this type of query. Secondly, to confine such an assessment to the large agencies could be misleading because a disproportionate amount of research on rare diseases might be supported by smaller agencies or industrial sources less readily accessible. We therefore decided not to approach primarily the grant givers but instead the recipients of such grants. We found that 4 (out of 16 existing) medical faculties in Germany publish detailed annual research reports on the internet, namely those of the Humboldt-University Berlin (Charité), Albert-Ludwigs-Universität Freiburg, Justus-Liebig-Universität Gießen, and Hannover Medical School (the only stand-alone medical faculty in Germany). For convenience, we restricted our assessments to these four faculties. We identified all research projects on rare diseases in these reports (2005 in Freiburg and Gießen, and 2006 in Berlin) by manual search for keywords associating a project directly and specifically with a disease listed in the Orphanet database of rare diseases.

In a first attempt, questionnaires were sent out to the leaders of all identified projects. These questionnaires were largely identical to those used at that time by country coordinators of Orphanet to assess national research activities, complemented by questions regarding grant givers and funding volumes. Although reminders were sent out to non-respondents after 2 months, the response rate remained low. In a second attempt, we therefore assessed the 2006 and 2007 annual research reports of Hannover Medical School (these reports collect data submitted by project leaders) and initially approached all project leaders. In accordance with previous experience (see above), responses by individual project leaders were unsatisfactory. For this reason we asked the research administration of Hannover Medical School to supply data on the amount of funds actually spent for each project in these 2 years. It was thus possible to obtain 100% ascertainment of all relevant projects. Years 2006 and 2007 were chosen because these were the most recent years for which overall medical funding statistics were expected to be available in Germany in 2010 (Landkarte-Hochschulmedizin website, www.landkarte-hochschulmedizin.de). In 2006 and 2007, Hannover Medical School ranked among the top three medical faculties in Germany with regard to measures such as

acquired external research funding per professorship or peer-reviewed publication record (Landkarte-Hochschulmedizin website, www.landkarte-hochschulmedizin.de).

Results and discussion

Results from questionnaires

We identified 305 projects on rare diseases in Berlin (Charité), 38 in Gießen, and 88 in Freiburg. Among all faculties assessed, namely Berlin, Gießen, Freiburg, and Hannover (see below), there were no major differences regarding the numbers of rare disease research projects per total external research funding (Landkarte-Hochschulmedizin website, www.landkarte-hochschulmedizin.de). Even upon reminders, response rates to questionnaires sent out to project leaders remained disappointingly low, comprising 4%, 5%, and 18%, respectively. No attempts were made to draw any conclusions from the responses from Berlin and Gießen. The total volume of funding for reported rare disease research in Freiburg amounted to 808,023 € (in 2005), i.e. rare disease research would receive 11.9% of total external medical research funding (37.8 million €; Landkarte-Hochschulmedizin website, www.landkarte-hochschulmedizin.de), assuming that the answers were representative. This is, however, likely not the case. It can rather be speculated that (better) funded projects are overreported.

Rare disease research at Hannover Medical School in 2006 and 2007

By scrutinizing the research reports of Hannover Medical School (MHH), we identified altogether 150 research projects on rare diseases in 2006 and 147 in 2007. Of these, 38 projects in 2006 and 43 projects in 2007 were in fact clinical studies (mostly on rare cancer therapies). These clinical studies were not included in the subsequent analyses regarding volumes and sources of funding because such studies, while listed in the research reports, are not included in the MHH internal database of external funds, and are also not contained in the nationwide assessments of third party research funding in Germany (Landkarte-Hochschulmedizin website, www.landkarte-hochschulmedizin.de). In Table 1, the data are stratified by “centers,” comprising clinical and/or theoretical departments grouped by clinical and/or research orientation, most of which are obvious by name, with the remaining easily identifiable on the MHH homepage. Table 1 groups funded projects into three categories: oncological diseases, cystic fibrosis (the single non-oncologic condition receiving the highest amount of funding), and all other diseases.

Table 1 Rare disease research activities and funding at Hannover Medical School 2006/2007

Center	2006				2007			
	Active projects	Funded projects	Funding (€)		Active projects	Funded projects	Funding (€)	
			Public	Charities			Public	Others
Oncology								
Biochemistry	0	0	0.00	0.00	1	1	0.00	72,069.68
Service units	1	0	0.00	0.00	0	0	0.00	0.00
Surgery	2	1	0.00	0.00	3	1	0.00	11,786.61
Internal medicine	20	10	125,897.82	683,226.52	13	7	102,023.72	173,401.78
Pediatrics	12	7	168,629.62	29,081.67	16	9	277,673.39	48,790.36
Pathology, forensics, genetics	8	2	10,117.00	54,600.00	4	4	197,697.00	79,245.88
Pharmacology, toxicology	1	0	0.00	0.00	0	0	0.00	0.00
Clinical chemistry	0	0	0.00	0.00	1	0	0.00	0.00
Physiology	3	2	66,124.62	0.00	3	3	117,253.47	0.00
Sum	47	22	370,769.06	766,908.19	41	25	694,647.58	50,496.22
Cystic fibrosis								
Pediatrics	8	3	60,662.37	0.00	7	2	28,475.80	0.00
Pathology, forensics, genetics	1	0	0.00	0.00	1	0	0.00	0.00
Internal medicine	3	3	110,000.00	4,000.00	2	2	110,000.00	4,000.00
Sum	12	6	170,662.37	4,000.00	10	4	138,475.80	4,000.00
All other projects								
Anatomy	5	4	0.00	25,508.37	6	6	0.00	34,924.05
Internal medicine	9	7	340,451.12	46,000.00	4	3	61,120.00	500.00
Pediatrics	17	10	495,233.68	0.00	18	9	434,914.45	101,535.36
Biometrics, medical informatics	1	0	0.00	0.00	0	0	0.00	0.00
Public health	1	0	0.00	0.00	0	0	0.00	0.00
Pathology, forensics, genetics	9	2	10,500.00	0.00	7	3	21,000.00	1,750.00
Radiology	2	1	0.00	0.00	1	1	0.00	35,181.33
Dermatology	0	0	0.00	0.00	1	0	0.00	0.00
Neurology	4	1	12.50	0.00	11	6	12.50	31.00
Psychological medicine	3	2	0.00	14,111.11	3	2	14,444.44	0.00
Surgery	1	0	0.00	0.00	1	0	0.00	0.00
Gynecology, obstetrics	1	1	54,257.62	0.00	1	1	2,736.53	0.00
Sum	53	28	900,454.92	85,619.48	53	31	534,227.92	139,008.69
Total	112	56	1,441,886.35	856,527.67	104	60	1,367,351.30	189,504.91

Total external funding for rare diseases research was 2.44 million € in 2006 and 1.97 million € in 2007. The relative shares of public, charity, and other (mostly industrial and donations) funding were 59.0%, 35.2%, and 5.7% in 2006, and 69.5%, 20.8%, and 9.6%, respectively, in 2007; this is consistently in contrast to the relative shares of these sources in overall medical research funding, in particular regarding the much more important role of charities and the much smaller role of other sources, in particular industrial, in rare disease research funding (Table 2). The average funding per project and year was 43,580 € in 2006 and 32,822 € in 2007. The average funding per project and year varied substantially depending on the source of funding. In 2006 (2007) the average funding by public, charity, and other sources was 55,457 € (59,450 €), 45,080 € (19,641 €), and 12,913 € (11,844 €), respectively.

The figures for total external research funding at Hannover Medical School are reported in Landkarte-Hochschulmedizin website (www.landkarte-hochschulmedizin.de). Funding for rare disease research at Hannover Medical School thus comprises 5.8% of all research funding in 2006, and 3.8% in 2007 (Table 2). It should be noted, however, that our survey did not assess funding of basic research, from which both rare and common diseases might benefit, nor the impact of rare disease research for common disorders or vice versa.

A striking, yet in view of public awareness of the overall health impact of malignant conditions, not completely unexpected finding was the high relative funding of research for rare cancers. In 2006, 48.0% and in 2007, 56.8% of all rare disease research funding went into research projects on rare cancers. It is estimated that the prevalence of rare cancers in Europe is 0.5% (rarecancers website, <http://www.rarecancers.eu/>). Thus, about half of all funding is invested into research of conditions comprising less than one tenth of overall rare disease morbidity.

Finally, an attempt should be made to put rare disease research funding into the perspective of overall morbidity. Is rare disease research receiving a “fair” amount of

funding? This question is difficult to answer, because overall morbidity estimates are typically based on self-reporting, whereas available estimates of rare disease prevalences are based on bibliographical research (www.orpha.net/orphacom/cahiers/docs/GB/Prevalence_of_rare_diseases_by_decreasing_prevalence_or_cases.pdf), and are not weighted here subjectively. The Robert-Koch-Institut, the leading institution for epidemiological assessments in Germany, performs regular population-based surveys. Around 20% of respondents currently regard their health status as less satisfactory or bad (Robert-Koch-Institut website, http://edoc.rki.de/documents/rki_fv/reJBwqKp45PiL/PDF/24aj8tYVir1Lo_14.pdf). If this figure is being taken as a crude estimate of overall morbidity (overall disease prevalence), rare disease prevalence being estimated to comprise 5–8% of the population, a huge discrepancy emerges: Rare diseases would cause about one third of the disease load but receive only between 4% and 6% of relative research funding. As noted above, this discrepancy is much inflated for the non-cancer conditions.

Conclusions

This case study is the first attempt to identify individual and cumulative research endeavour on rare diseases in Germany with a focus on one single medical faculty, Hannover Medical School. It appears to be the first of this kind globally. This study can only be considered as a pilot project and needs to be complemented by similar studies elsewhere in order to lead to a reliable picture, from which one might be able to generalize. However, our data already indicate enormous deficits and inequities in rare disease research. We would like to appeal to both researchers and granting agencies to contribute to future assessments of the rare disease research landscape, and to improve the situation should our alarming findings be confirmed. Such monitoring should aid in measuring direct and indirect effects of national and international rare disease research programmes such as the German Federal Ministry of

Table 2 Medical research funding at Hannover Medical School, 2006–2007

	Public sources	Charities	Others	Total
2006	Total funding 22,900,000 € (54.4%)	Total funding 3,830,000 € (9.1%)	Total funding 15,360,000 € (36.5%)	42,090,000 €
2006	RD funding 1,440,000 € (59.0%)	RD funding 860,000 € (35.2%)	RD funding 140,000 € (5.7%)	2,440,000 € (5.8%)
2007	Total funding 29,130,000 € (56.6%)	Total funding 4,310,000 € (8.4%)	Total funding 18,070,000 € (35.1%)	51,510,000 €
2007	RD funding 1,370,000 € (69.5%)	RD funding 410,000 € (20.8%)	RD funding 190,000 € (9.6%)	1,970,000 € (3.8%)

Public funding comprised funding through state and federal sources, the European Union, and the Deutsche Forschungsgemeinschaft
RD rare disease research

Education and Research (BMBF) networks (2003–2016) in Germany (BMBF, programme on rare disease research, www.bmbf.de/de/1109.php) and E-Rare (2006–2010) as well as E-Rare 2 (2010–2014) in Europe (European Commission E-Rare programmes, www.e-rare.eu).

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Declaration of competing interests The authors declare that they have no competing interests.

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