

# From Mass Testing to the Fate of Individuals

**Claus Peter Müller-von der Grün**

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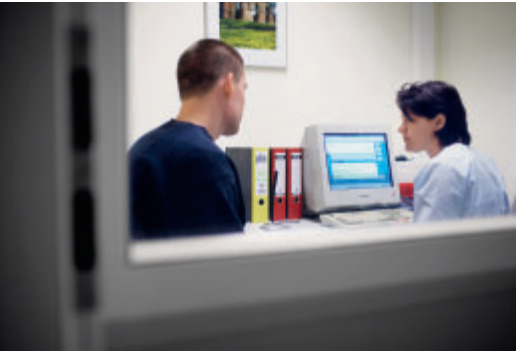
We are relatively sure about what we categorize as 'sick,' and we define the limits of what we consider 'healthy.' But what is 'normal?' The scientists at the Institute of Community Medicine at Ernst Moritz Arndt University of Greifswald are trying to answer this question. They look at the whole picture in order to help the individual. The Institute of Community Medicine is unlike any other in Germany.

By Claus Peter Müller von der Grün





The ruins of Eldena monastery became famous through paintings of romantic artist Caspar David Friedrich. Today, Heyo K. Kroemer, PhD, Dean of the College of Medicine, can proudly look back at 550 years of academic tradition at Ernst Moritz Arndt University.



Examinations for SHIP 2 will include interviews, a dental status, ultrasound and MRI exams, ECGs, lab tests, and even a night under sleep-lab conditions, among many other tests.



“So far, people have been over- or undertreated. They are treated incorrectly, because they are not treated individually.”

Heyo K. Kroemer, PhD, Dean, College of Medicine,  
Ernst Moritz Arndt University, Greifswald, Germany

Greifswald is located in Northeastern Germany. Even in its own state, Mecklenburg-Western Pomerania, the city is a border town on the Baltic Sea. Its architecture alludes to its former wealth as a Hanseatic City – but that is now in the past. Today, Mecklenburg-Western Pomerania has structural problems. The industrial sector is almost nonexistent, and the population density is relatively low. What is even worse, its population is dwindling and therefore mean age is increasing faster than the German average. At the time of German reunification after the collapse of the socialist systems in Europe nearly two decades ago, Mecklenburg-Western Pomerania statistically had the youngest population among the 16 federal states in Germany. Today, the average age in Mecklenburg-Western Pomerania lies two years above the German average – which has grown by two to three years in the last two decades as well. This development is typical for many countries. Italy has already aged into a gerontocracy, and the politics of a one-child family will turn China into an empire of the old.

### **Mecklenburg-Western Pomerania as an Example**

Mecklenburg-Western Pomerania is an example for numerous regions of this

world. It is difficult to maintain the infrastructure in sparsely populated areas. Unfortunately, when reducing the choice of schools, train connections, or doctor's offices, the region further loses attractiveness. At the same time, people's needs and their medical requirements change with age. Based on the demographic change alone, the number of patients suffering from cancer or from a stroke in Mecklenburg-Western Pomerania will increase by approximately 30 percent by the year 2020, according to Wolfgang Hoffmann, MD, Head of the Department for Epidemiology of Health Care and Community Health. The number of dementia cases will increase by 60 percent – while the population will have decreased by another 15 percent. This trend appears to be rapidly spiraling downward. The College of Medicine at the University of Greifswald wants to become a safe harbor. It wants to support its region and show that regions with similar problems, at home and abroad, can learn from its experience. The fact that the College of Medicine in Greifswald was preserved after the fall of the Berlin Wall did not go without saying. After quite some discussion, the German Science and Humanities Council decided to keep the university with more than 550 years of tradition. And those

responsible for the medical faculties took advantage of this opportunity.

### **Community Medicine Opens Unimagined Prospects**

Dean Heyo K. Kroemer, PhD, looking back with a touch of irony, recalls that they decided, on a “type of barefoot medicine,” as compared to expensive high-tech clusters at other universities. They opted for community medicine. The people at Greifswald wanted to deal with diseases that were prevalent in the vicinity of the university, a region of more than 200,000 inhabitants around the cities of Greifswald and Stralsund. “That's where we differ from public health, where theory takes center stage more often than it does for us,” adds Hoffmann to prevent possible misunderstandings. The scientists at the University of Greifswald perform real-life research. They want to know how people in Pomerania are doing.

“It's relatively easy to find sick people, and illness is easier to identify than perfect health. So we asked ourselves, ‘how do we find healthy people?’” says Matthias Nauck, MD, Head of the Lab of Clinical Chemistry at the University Hospital.

In 1995, scientists began to develop a concept for the Study of Health in Pomer-

ania (SHIP). During SHIP 0, basic data was to be acquired from citizens of the cities Stralsund, Greifswald, and Anklam. This way, scientists would be able to not only detect relationships between frequent medical and dental diseases, but also their possible sources. In addition, they wanted to investigate the population's attitudes toward prevention and health-care.

The scientists were looking for representative volunteers for the study. They did not want to examine patients, but to introduce clinical medicine to the population to evaluate their health status. Of course, from the very beginning the scientists were aware of their responsibilities toward every single volunteer. If they were to find indications of a disease according to the current state of knowledge, the respective volunteer would be informed and asked to get in touch with his private practitioner. The general physician would then carry out the necessary examinations and decide on further treatment.

The people in Greifswald convinced their own state government as well as the German Federal Ministry of Education and Research of the importance of the project. The latter integrated the study into the program for promoting clinical research in the new federal states. Beginning in 1996, potential volunteers were selected using the data from the registration office.

For the study, 7,008 women and men between 20 and 79 years of age were contacted. The population of the region of study was approximately 212,000 in 1997. Close to 70 percent of the people notified came back to the university and agreed to participate in the SHIP study. The feedback was unusually high and would probably not have been possible in any other region in Germany. The trust of the people in Pomerania toward state-run facilities and those rich in tradition is clearly great. Between October 1997 and May 19, 2001, 4,310 people took part in extensive examinations, each of them taking about six hours.

In two interviews, the respondents provided information with respect to chronic illnesses, sociodemographics and pro-

fession, medical aid, and their health behavior. During a thorough dental examination, 1,000 variables in the oral cavity alone were acquired for each volunteer. Thyroid, liver, gallbladder, and the vessels supplying the brain were examined with ultrasound. Blood and urine samples were drawn from the patients. Blood pressure and body measurements were quantified precisely.

### Extended Follow-up Studies

The scientists extended SHIP 0 to a follow-up study: SHIP 1. From October 23, 2002 to September 1, 2006, 3,300 healthy volunteers returned to the university to be examined in a second round. As compared to the first data acquisitions, additional genetic analyses, a lung function test, and an examination for skin cancer were added. Using an electrocardiogram (ECG), the scientists looked for possible cardiac arrhythmias. A tele-ECG and a stress-ECG provided information about the conditions of the patient in everyday life and under bodily stress. Finally, the volunteers' legs were subjected to a venous diagnosis.

The third round of examinations started in March 2008 and will run for the next three years. From the very first cohort, 3,420 volunteers are still alive. Approximately 8,000 new potential volunteers will be added via a representative random sampling. At the same time, the scientists will start a "morbidity follow-up," Hoffmann reports. They will ask the volunteers which diseases they are suffering from since the previous screening. With the volunteers' permission, they will also ask for information from the treating physicians. For volunteers who died, the cause of death is recorded.

The inquiries for SHIP 2 will be even more extensive than the previous data acquisitions. The questioning and examining will take a total of ten hours per volunteer. Nights at the Greifswald Park Hotel have also been added, where volunteers will stay in conditions similar to a sleep lab to determine the prevalence of sleeping disorders such as the feared sleep apnea.

As compared to SHIP 1, whole-body examinations in a MAGNETOM® Avanto

magnetic resonance imaging (MRI) system have been added. The system, valued at €1.5 million, was made available by Siemens for three years, exclusively for the examination of SHIP volunteers. The MRI method does not subject people to radiation exposure. It enables detail visualization of one cubic millimeter size and makes certain organs visible for the first time within SHIP, which until now relied on ultrasound for imaging. "Gallstones are recognizable with MRI when they are formed. Ultrasound is not the standard procedure when visualizing the pancreas, but it can certainly be done with MRI. In any case, depending on the organ or tissue you want to visualize, the boundaries of organs can be clearly defined with MRI," says Hoffmann.

### MRI Completes the Equipment

Ralf Puls, MD, supervises SHIP-MRI as a member of the Greifswald Department of Radiology. From his point of view, MRI ideally completes the equipment available at Greifswald: the genome and the metabolome project. The genome, decoded with DNA analysis, includes the blueprint for the proteins – the true building blocks of life. And proteins, in turn, determine the metabolism which can be read from the metabolites derived from the blood and waste products of humans, known in their entirety as metabolome. In a complex way, metabolism and the structures of the organism affect one another alternately. Diabetes may lead to a fatty liver, while a fatty liver could in turn determine the course of diabetes. Lastly, changes in the finest of structures are measured highly accurately with MRI.

### Siemens Helps Greifswald to Evolutionize Medicine

Siemens considers itself as challenged as the scientists at the university. By building up the database together with the scientists at Greifswald and converting the information gained into medically useful knowledge with performance-oriented information technology, Siemens is opening up new possibilities to increase the quality of healthcare and to reduce costs. It is vital to seamlessly include all



All volunteers' samples are barcoded and then frozen at minus 80 degrees Celsius to enable testing of possible future hypotheses.



“We are really entering uncharted territories.”

Wolfgang Hoffmann, MD, Director, Institute of Community Medicine, Section Epidemiology of Health Care and Community Health, Ernst Moritz Arndt University, Greifswald, Germany



processes, from prevention, via diagnostics and therapy, to aftercare.

To examine volunteers this extensively, to evaluate their samples and measurement data as well as to store them and link them together to arrive at the correct results, requires gigantic logistic coordination as well as technical efforts. It begins with securing the power supply for the MRI equipment and ends with the calculation of energy costs for the armada of processors required to evaluate the entire data, which reaches up to €15,000 a year. Additional costs include the creation of the necessary infrastructure, the planning of examinations, the on-the-job training of personnel, the organization of processes, and the lab set-up. Finally, the volunteers have to be taken care of responsibly, because for the scientists at

Greifswald, ‘their’ volunteers are people and not just numbers.

### Live Interdisciplinarity

The diversity of professions in the project team attests to its interdisciplinarity. Fifteen information scientists, statisticians, educators, psychologists, biomathematicians, medical documentarists, demographers, and biochemists work at the organization’s center, headed by Assistant Professor Henry Voelzke, MD, and statistician Dietrich Alte, PhD.

In the meantime, the Examination Center was created in the Medical Supply Center of the University. Headed by human biologist Nicole Aumann, PhD, 14 employees care for the volunteers, among them physicians, medical-technical assistants, nurses, and physician assistants. The

first interviews and examinations in the Examination Center will take between four to six hours per volunteer. The procedure begins with filling out forms and moves to ultrasound, glucose tolerance tests, blood samples, and a dental examination, including an interview. These are followed by a general interview and function tests. They may include, for example, an ocular fundus and a body impedance analysis.

### The Highly Automated Reference Lab

A few meters away, a new building houses a modern, highly automated lab – a Siemens reference lab. Lab head Nauck evaluates the equipment as “absolutely efficient.” Automation via a lab line allows the processing of numerous samples



“It’s relatively easy to find sick people, and illness is easier to identify than perfect health.”

Matthias Nauck, MD, Director,  
Institute for Clinical Chemistry and Laboratory Medicine,  
Ernst Moritz Arndt University, Greifswald, Germany



without requiring that the blood samples be touched by human hands. Currently, five analysis systems connected to the StreamLAB® Analytical Workcell are used to determine more than 150 different analytes. The blood samples are automatically centrifuged and the covers of the test tubes are removed. Subsequently, the samples are distributed to the various devices, where the blood sera are taken from the analysis devices, and the chemical reactions are started. The test tubes are returned immediately to the conveyor belt to ensure that further requested analyses are started at the next analysis devices while the other evaluations are still running. After an hour, all results are available onscreen at the workstations, because “We are becoming a paperless hospital,” says Dean Kroemer. The univer-

sity has expanded the lab infrastructure for the SHIP 2 study. When 15 volunteers are to be examined daily in the future, 750 aliquots (partial samples) have to be provided with a barcode and then frozen, because all samples are conserved and archived. In special containers, which protect the biomaterial from drying out, they should be preserved as long as possible at minus 80 degrees Celsius. If the past and future SHIP examinations lead to the need for generating new research hypotheses, the samples have to be ready to test them.

### Looking Back at Data Allows a Look into the Future

By reversing the perspective, looking back at the lives of thousands of people recorded in detail will be like looking

into the future. It will help solve many puzzles that appear in the course of diagnosing an illness and projecting its course. Some of the puzzles have already been solved by the scientists in Greifswald because of the available data from two SHIP investigations. They will be able to provide even more answers when the data from SHIP 2 are evaluated. But prior to solving a puzzle, one has to be set first. The scientists compare the results of SHIP studies 0, 1, and soon 2 to find distinctive features. They form working hypotheses when a connection seems plausible, but they also work together with Siemens on datamining. Nonjudgmental and without any ulterior motives, the computer looks for statistically significant relationships between the most widely different phenomena.

## SHIP at a Glance

### Challenge:

"Individualized medicine suffers from the absence of standards," says the Dean of the College of Medicine of Ernst Moritz Arndt University of Greifswald, Heyo K. Kroemer, PhD, Professor of Pharmacology.

### Solution:

The scientists of the Institute of Community Medicine in Greifswald examine thousands of volunteers, putting them through their paces, but also report their social and psychic well-being. The approach is interdisciplinary and holistic, technically based and empirical. Since the scientists are currently surveying the status of health of the same people for the third time at five-year intervals, they not only determine how sick or healthy the population really is. They also recognize how the risk factors solidify, how a disease develops over the years, and the course it takes under which individual circumstances. Last but not least, the scientists are looking for an algorithm to find those very few characteristics under millions of variables of the collective examined which allow the prediction and prevention of an imminent disease in an individual case.

### Result:

The examinations did create knowledge: They showed, for example, that every fifth adult in the most Northeastern German state suffers from a fatty liver and that gallstones occur frequently. Without a doubt, the Study of Health in Pomerania (SHIP) is one of the internationally outstanding epidemiological studies.

SHIP 0 and 1 have already enriched the sciences. The examinations revealed, for example, that every fifth adult in the most Northeastern German state suffers from a fatty liver, says Voelzke, the manager of the SHIP project. A fatty liver is a frequent ultrasound diagnosis. The risk factors are excessive weight, malnutrition, and above average alcohol consumption. Until a few years ago, explains Voelzke, a fatty liver was estimated as an "insignificant accidental finding." Only most recently, proof has been provided, due to the large epidemiological studies, that people with a fatty liver have an increased risk for diabetes and myocardial infarction. The SHIP study is one of the very few population studies worldwide

where the liver is examined via ultrasound.

### Research is Not an End in Itself

Research is not an end in itself. Instead, the examination results challenge to estimate the outcome of the findings and to draw conclusions. "People with a fatty liver," says Voelzke, "cause 26 percent higher expenditures for medical treatment as compared to people without this diagnosis." These people have to do something for their health, and not for the costs alone. They have to reduce their risks. They should eat healthier, exercise more, and drink less. Even more than before, ultrasound examinations of the liver should be used as preventive

measure. Gallstones are also quite frequent in Western Pomerania. In every second woman age 60 to 80 years, a gallstone is found with ultrasound, or she has already had gallstone surgery. In SHIP, known risk factors such as excess of weight or lack of exercise can be identified. However, there are also genetic factors which play a role and can partly explain the exceptionally high frequency of cholelithiasis in the area.

Once more, the SHIP study displays that medicine has to look at a human being holistically as a subject within a social and political system. Narrative-based, as well as technology-based medicine, are not opposites but rather necessary parts of the whole. The psychiatric screening showed that 200 volunteers continue to suffer from posttraumatic stress syndrome as a long-term consequence of political pressure and massive personal threats under the socialist dictatorship.

### "We are really entering uncharted territories"

Are we looking at a scientific leap forward? "We are really entering uncharted territories," responds Hoffmann. He is surprised at how much the combination of diseases among older, multimorbid volunteers changes from individual to individual. For example, among the more than 1,100 patients involved in another study by the department, there is not a group with more than three patients who suffer from the same combination of different diseases, such as, for example, diabetes, Parkinson's, and stroke.

The scientists have to filter out the decisive factors from the abundance of data. Says Hoffmann: "We will have more than 10, 15, or 20 million variables that are of interest for a particular patient. We have to find an algorithm to allocate the correct variable for every single question. Currently, we are scrubbing thousands of analyses," to determine whether diseases and genetic imprinting are interconnected. Only after this work is completed do the scientists dare to approach more complex prognoses.

The SHIP study changes the effects of medicine toward the individual as well as its interactions with other disciplines

at the university and the world outside the sciences. "So far," continues Kroemer, "people have been over- or undertreated. They are treated incorrectly, because they are not treated individually." Due to their genetic dispositions, some individuals are not able to absorb certain active ingredients that alleviate pain or cure diseases. The required effective level does not build up in the organism of these people. Others absorb the active ingredient too quickly, resulting in an overdose. The SHIP study will help scientists to use genetic information to differentiate between people who can be helped under certain situations and at what level of likelihood, and those who cannot – and above all, how to best help individual patients. This makes for a more effective treatment and also reduces costs. No one in Greifswald wants to dispute that the cooperation with economists is useful, because money is too precious to simply squander. But to consider costs alone comes up short. What truly counts is quality. Medicine can be improved because it helps in a more targeted manner. As a result, new ethical questions arise. Kroemer does not deny them: "Should a person be treated with medication if it only helps at a ten percent probability? We come up against those questions quickly and rely on the Philosophical and Theological College of our university. That is another quality of a small university."

### The Medical Paradigm in a State of Flux

Hoffmann sees the medical paradigm in a state of flux. Today the patient is sick, goes to the doctor and expects, in the ideal case, to become healthy again. In the future, especially in an aging society, the effect will be on abatement, or, as we call it today, symptom management, rather than full recovery. Medicine will help the individual to maintain his or her own resources, to mobilize and participate in the social life around him or her as best as possible. It is up to the individual. "What does the patient want?" asks Hoffmann: "Does he want to dance or read? What should be treated first: his high blood pressure or his incontinence?"

It is rare to find an 80-year-old without a diagnosis. "In real life, it is the older patient in particular who suffers from three to five different diseases. But the right therapies for each of these diseases frequently do not fit together and lead to interactions and side effects," says Hoffmann. Those over 80 years old take an average of eight medications a day. But it is often a problem to take more than three, according to gerontologists – because forgetfulness of the patient pairs with interactions among the drugs. "This means that for medical reasons alone, it is impossible to treat everything at the same time – not only because of economics," says Hoffmann.

### Individualized Prevention

To more effectively apply ever-limited finances, the risk profile of the individual must first be determined and the measurement methods refined. This will make the probability to predict which disease will occur much more accurate than in the past. The experiences made with individualized therapy have to be integrated into the treatment strategy. From there, individualized prevention arises in the

next step, so that the prognosis does not occur despite the prediction. This is frequently the – welcomed – fate of unerring prognoses. They prevent their occurrence by arousing the warned so that they repent or intervene. This applies to large and small matters. Western Pomerania will not overcome all structural weaknesses or turn the demographic change around, but the bitter prognoses yield results. Due to the conservation of the College of Medicine of the Ernst Moritz Arndt University and the courage to commit to Community Medicine, Greifswald has become an attractive academic location for young people, for the international community of researchers, and for strategically acting high-tech companies.

*Claus Peter Müller von der Grün is an editor at Frankfurter Allgemeine Zeitung. Since he joined the publishing house in 1986, he has consistently dealt with questions addressing healthcare policy and the healthcare industry.*



The university has expanded its equipment to also be able to analyse metabolites via nuclear magnetic resonance spectroscopy.

### Further Information

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Responsible for Contents: Dr. Stephan Feldhaus

Director of Customer Communications: Silke Schumann

Chief Editor: Doris Pischitz

Editorial Team: Gabriela Castelo, Sonja Fischer,

Timo Schickler, Sibylle Schikora, Katja Stöcker,

Abigail Weldon

Editorial Assistance: evolvo marketing gmbh

Production: Norbert Moser

All at: Henkestrasse 127, D-91052 Erlangen, Germany

Phone: +49 9131 84-7529, Fax: +49 9131 84-4411

email: editor.medicalsolutions.med@siemens.com

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