Datenbank genomischer Varianten für die klinische Anwendung
und die diagnostische Forschung
TMF-Workshop, Berlin, 7. Dezember 2012

Erwarteter Nutzen einer Datenbank genomischer Varianten von gesunden und kranken Personen

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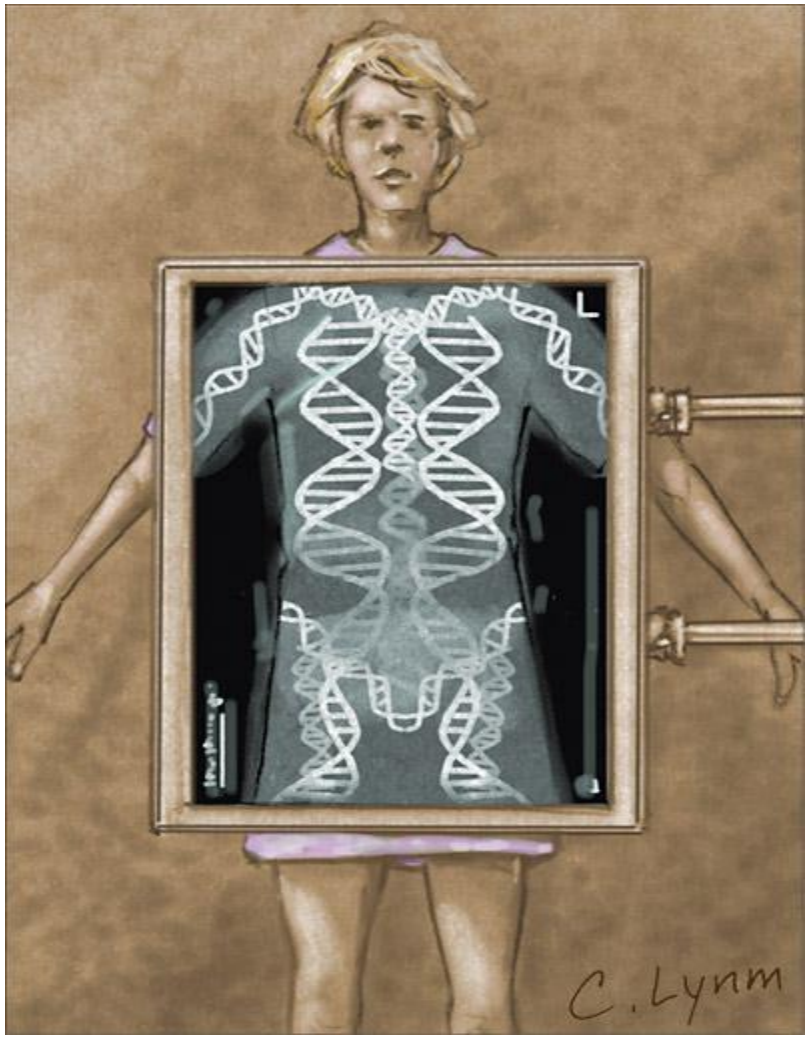
NGS

next generation sequencing

Camille Flammarion, *L'Atmosphère. Météorologique populaire;* Paris 1888



Diagnostik

auf der genetischen Ebene:

Charakterisierung von

DNA-Sequenzvarianten

NGS

next generation sequencing

WGS

whole genome sequencing

WES

whole exome sequencing

PES

partial exome sequencing

Cell

Leading Edge
Essay

Genetic Heterogeneity in Human Disease

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DOI 10.1016/j.cell.2010.03.032

Strong evidence suggests that rare mutations of severe effect are responsible for a substantial portion of complex human disease. Evolutionary forces generate vast genetic heterogeneity in human illness by introducing many new variants in each generation. Current sequencing technologies offer the possibility of finding rare disease-causing mutations and the genes that harbor them.

"Every unhappy family is unhappy in its own way," wrote Tolstoy in Anna Karenina. Tolstoy was reflecting on the individually unique nature of human tragedy. We suggest that this principle also captures the misfortune of human disease.

Pedigree: M 90 00 029 Gene: TLR10 HGNC:15634 Location: 4p14

Mutation: g.4:38,776,478G>T c.734C>A p.S245X

T/T

Datenbank Genomischer Varianten

Welchem Zweck soll/kann eine solche Ressource dienen?

- Referenzdaten für Diagnostik
- Referenzdaten für Forschung
- Zugang zu internationalen Konsortien

Datenbank Genomischer Varianten

Welchem Zweck soll/kann eine solche Ressource dienen?

- Referenzdaten für Diagnostik
- Referenzdaten für Forschung
- Zugang zu internationalen Konsortien

- *Stufenweises Vorgehen, schrittweise Implementation*
- *Zurückstellen von Partikularinteressen*
- *Verzicht auf Sonderfunktionen*

Datenbank Genomischer Varianten

There is no genetic diagnosis
(sensu strictu)
outside the framework of the
Mendelian paradigm

cf. Ken Weiss, TMF−School extra, Berlin, 24. bis 28. September 2012

Viele genetische Faktoren – begrenzte Effekte

TMF-School extra: Teilnehmer diskutieren über die realistische Einschätzung der Potenziale und Ziele genomischer Forschung

Präzise, beantwortbare Fragestellungen, adäquate Studiendesigns und die Fokussierung auf natürliche Experimente in humanen Populationen werden künftig wesentliche Erfolgsfaktoren der Genomforschung sein.

Der Unterschied zwischen detektierbaren und medizinisch relevanten genetischen Effekten ist groß, so die Dozenten: Die meisten genomweiten Assoziationsstudien der letzten Jahre hätten bestätigt, dass die realistisch zu erwartende Anzahl an genetischen Faktoren groß, aber ihre Effektstärke klein und ihr medizinisch-prognostisches Potenzial für die meisten humanen Erkrankungen gering sei.

Diese Folgerung zogen Teilnehmer und Referenten des Kurses „Logical Reasoning in Human Genetics“, der vom 24. bis 28. September 2012 als Extra-Ausgabe der TMF-School in Berlin stattfand.

Datenbank Genomischer Varianten

Wer hat mit einer solchen Ressource zu tun ?

- Benutzer, *User*
- Beiträger, *Contributor*
- Betreiber, *Operator, Management*

Datenbank Genomischer Varianten

Wer hat mit einer solchen Ressource zu tun ?

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KISS

Keep it simple, stupid!

genomeweb

July 13, 2012

NHGRI to Fund Resource of Clinically Relevant Variants

NEW YORK (GenomeWeb News) – The National Human Genome Research Institute (NHGRI) is planning to fund the creation of a single resource that would house and disseminate data about potentially clinically relevant genetic variants that are being unearthed by genomics research projects.

Centralizing Clinical Variants

November 07, 2012

Centralizing Clinical Variants

The National Center for Biotechnology Information's ClinVar database is proving useful for clinical labs trying to interpret genetic variants uncovered by next-gen sequencing, reports *Nature*.

ClinVar, designed to house information on the relationships between human variations and phenotypes, not only integrates clinical variation data from numerous publicly available resources, but "also provides, for the first time, a central place in which clinical testing laboratories can deposit their data," *Nature* says.

GENETICS

One-stop shop for disease genes

NIH database integrates data from clinical genetic testing labs and literature.

BY MONYA BAKER

”For everybody in the field, I think there will be a sigh of relief that this is finally happening,” says Stephen Kingsmore, who is using whole-genome sequencing to pin down genetic causes of rare diseases in newborns at the Children’s Mercy Center for Pediatric Genome Medicine in Kansas City, Missouri. He predicts that his team will turn to ClinVar every time it finds a mysterious variant in a patient sample.

Revised Concept **Clearance for RFA**

Clinically Relevant Variants Resource:

A Unified Approach for Identifying Genetic Variants for Clinical Use

NHGRI Advisory Council, May 2012

Purpose

The National Human Genome Research Institute (NHGRI) proposes to support a process for the identification and dissemination of consensus information on genetic variants relevant for clinical care. The goals of this initiative are to:

1) identify genetic variants with likely implications for clinical care and incorporate these variants and their supporting evidence into a resource that can serve as the substrate for development of practice guidelines by relevant professional societies and other stakeholders;
2) establish a process for transferring this information to appropriate clinical organizations for development of these guidelines; and
3) engage, coordinate and build upon existing programs and reduce duplicative efforts to identify such variants across numerous research and clinical organizations.

ClinVar Data Dictionary

Overview

This document defines the data elements represented in the ClinVar database. The document includes descriptions of how data are managed, the XML used to represent each concept, the field name in the spreadsheet version of the submission document, and allowed values. Not all values need be submitted; some will be reported based on information in NCBI's databases.

Most elements in the database are characterized with respect to the submitter, identifiers used by the submitter, date submitted, date modified, validity status, review status, and whether the data should be public or private. Rather than repeating these elements for each data category defined below, the word **Source/Status** will be used as a pointer to the Data source/Status section, where the source and status elements are defined.

Processing of NGS data

- aggregation into allele counts/frequencies
- aggregation into genotype counts/frequencies
- anonymization

EMERY
AND
RIMOIN'S

Volume 1

Principles and Practice of

MEDICAL GENETICS

FOURTH EDITION

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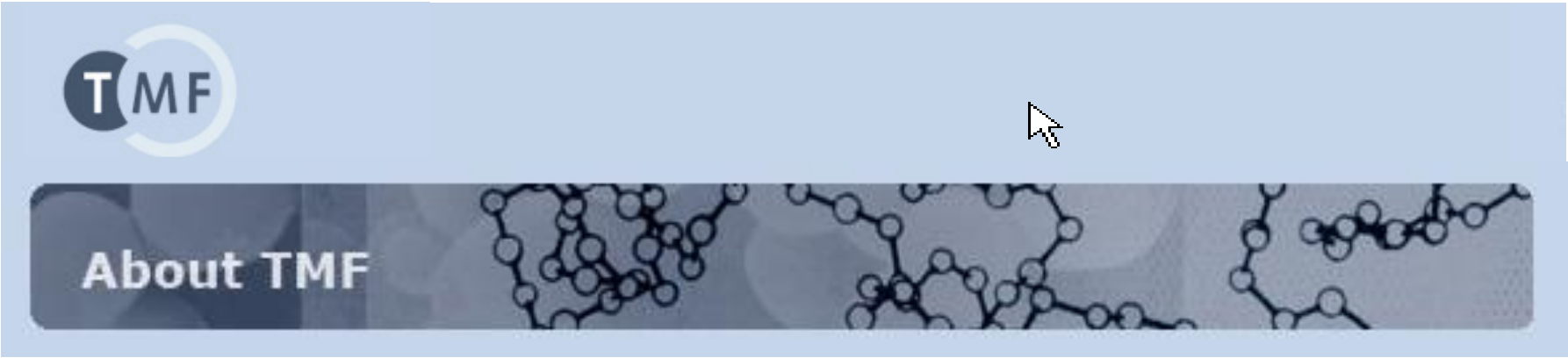
SECTION 4

APPROACHES TO SPECIFIC DISORDERS

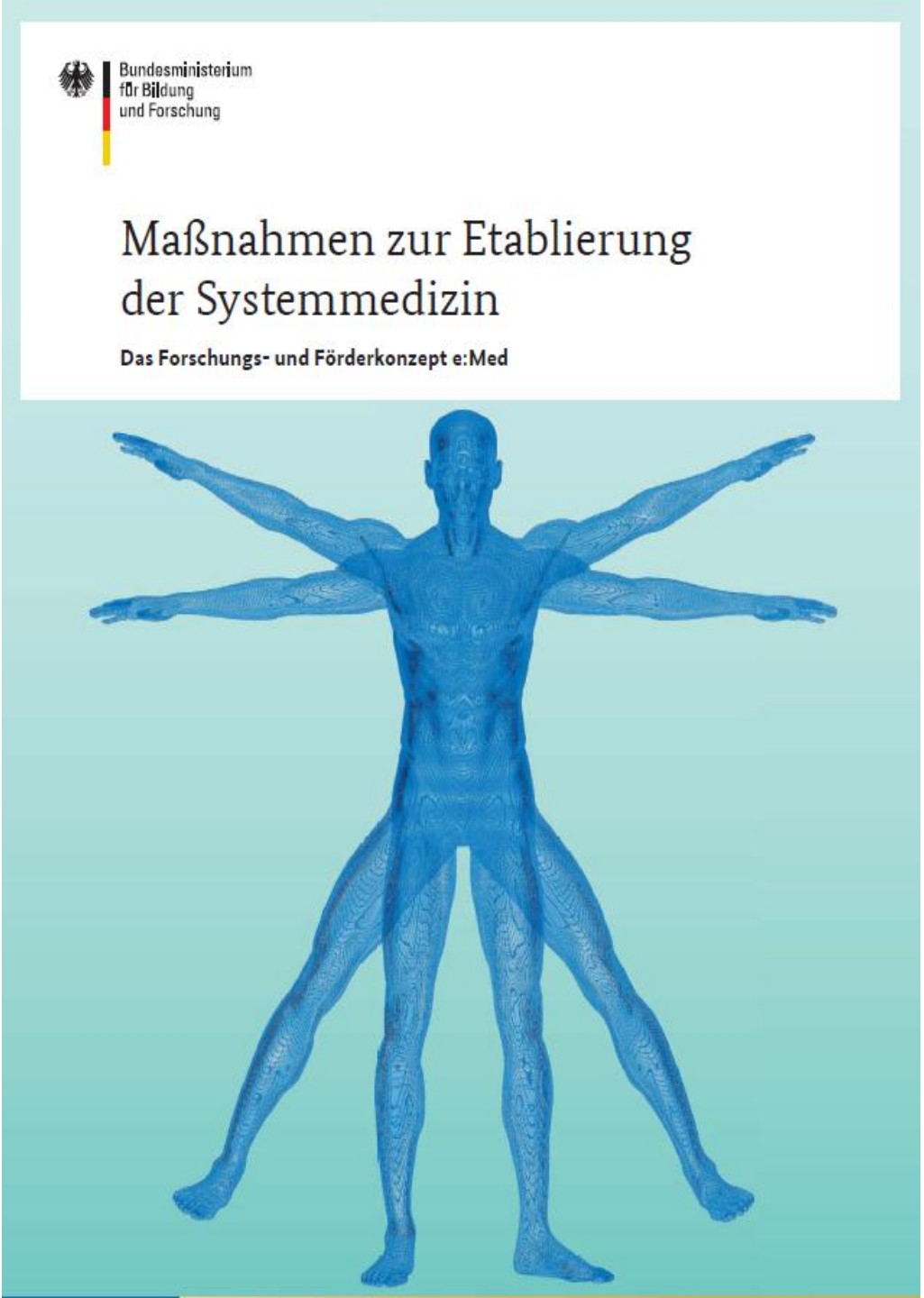
- Chromosomal disorders
- Cardiovascular disorders
- Respiratory disorders
- Renal disorders
- Gastrointestinal disorders
- Hematologic disorders
- Immunologic disorders
- Endocrinologic disorders
- Metabolic disorders
- Mental and behavioral disorders
- Neurologic disorders
- Neuromuscular disorders
- Ophthalmologic disorders
- Deafness
- Craniofacial disorders
- Dermatologic disorders
- Connective tissue disorders
- Skeletal disorders

17 Categories



Our Mission

We bring together researchers in different disciplines and develop concepts, infrastructures, and methods that promote medical research. We thus increase the safety, quality, and efficiency of medical research, ensure the necessary standardization, and offer researchers, irrespective of their scientific issues, assistance in dealing with the increasingly complex legal and regulatory infrastructure of medical research.



e:Med

Executive Summary pg. 3

… Die Systemmedizin braucht dazu nicht nur vielfältiges, sondern vor allem auch anwendungsgerecht aufbereitetes Datenmaterial – von Erbgutinformationen bis zum Blut- oder Röntgenbild.

SPECIAL ARTICLE | Genetics inMedicine

Managing incidental findings and research results in genomic research involving biobanks and archived data sets

Susan M. Wolf, JD[1], Brittney N. Crock, JD[1], Brian Van Ness, PhD[1], Frances Lawrenz, PhD[1], Jeffrey P. Kahn, PhD, MPH[2], Laura M. Beskow, PhD, MPH[3], Mildred K. Cho, PhD[4], Michael F. Christman, PhD[5], Robert C. Green, MD, MPH[6,7], Ralph Hall, JD[1]; Judy Illes, PhD[8], Moira Keane, MA[1], Bartha M. Knoppers, JD, PhD[9], Barbara A. Koenig, PhD[10], Isaac S. Kohane, MD, PhD[7], Bonnie LeRoy, MS[1], Karen J. Maschke, PhD[11], William McGeveran, JD[1], Pilar Ossorio, PhD, JD[12], Lisa S. Parker, PhD[13], Gloria M. Petersen, PhD[14], Henry S. Richardson, JD, MPP, PhD[15], Joan A. Scott, MS[16], Sharon F. Terry, MA[17], Benjamin S. Wilfond, MD[18] and Wendy A. Wolf, PhD[19]

INTRODUCTION

An ongoing debate focuses on the question of whether researchers bear duties to analyze and offer back to research participants incidental findings (IFs) and individual research results (IRRs) generated in genetic and genomic research.

GENETICS in MEDICINE | Volume 14 | Number 4 | April 2012

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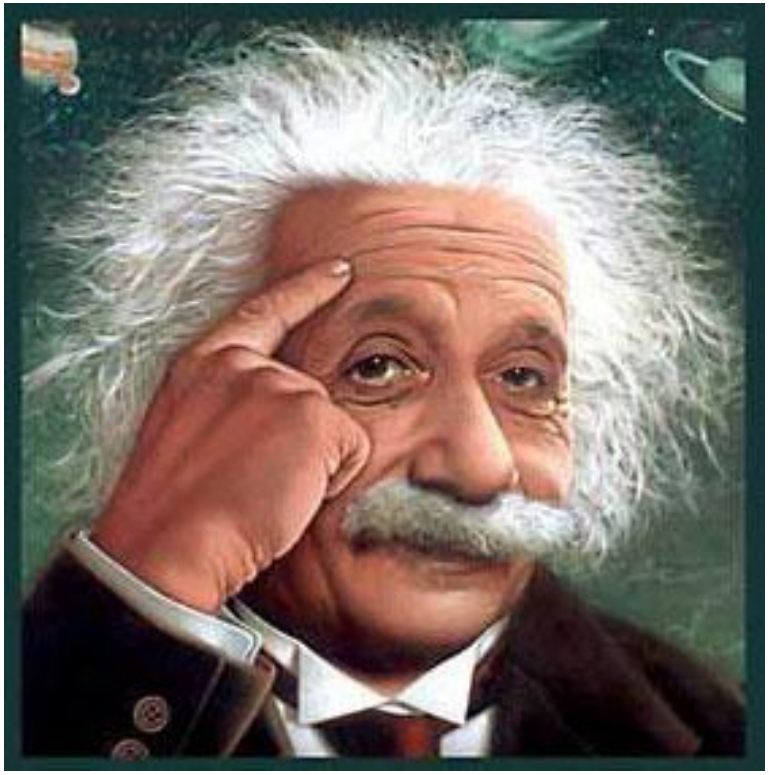
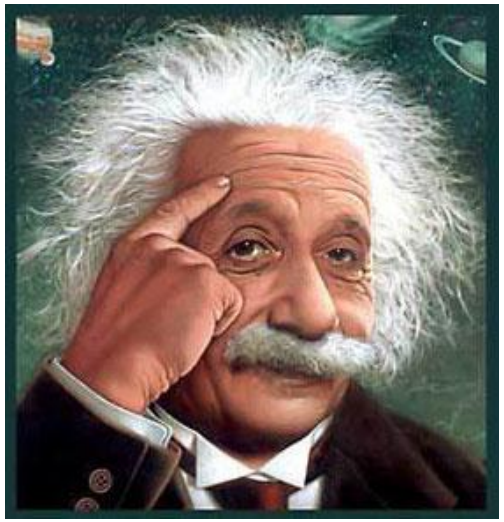


Albert Einstein (1879 – 1955)

Things should be made as simple as possible, but not simpler.



Vielen Dank fürs Zuhören !

Fragen werden gerne beantwortet !

TMF_Wienker_2012-12-07

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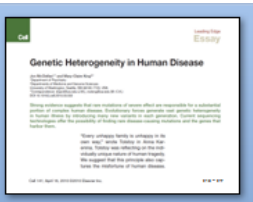

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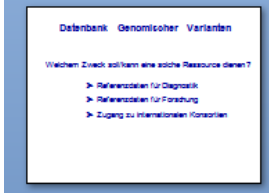

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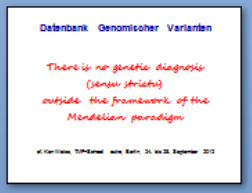

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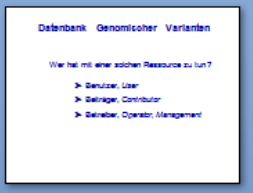

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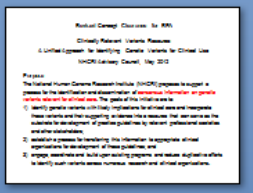
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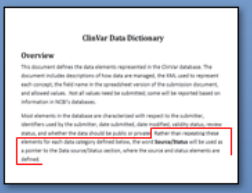

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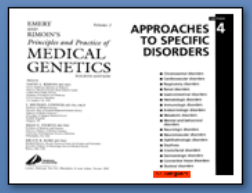

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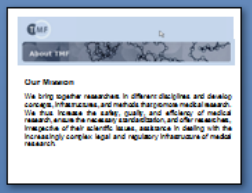

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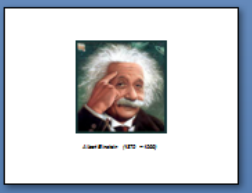
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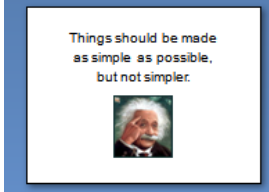

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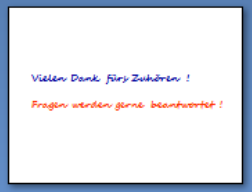

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