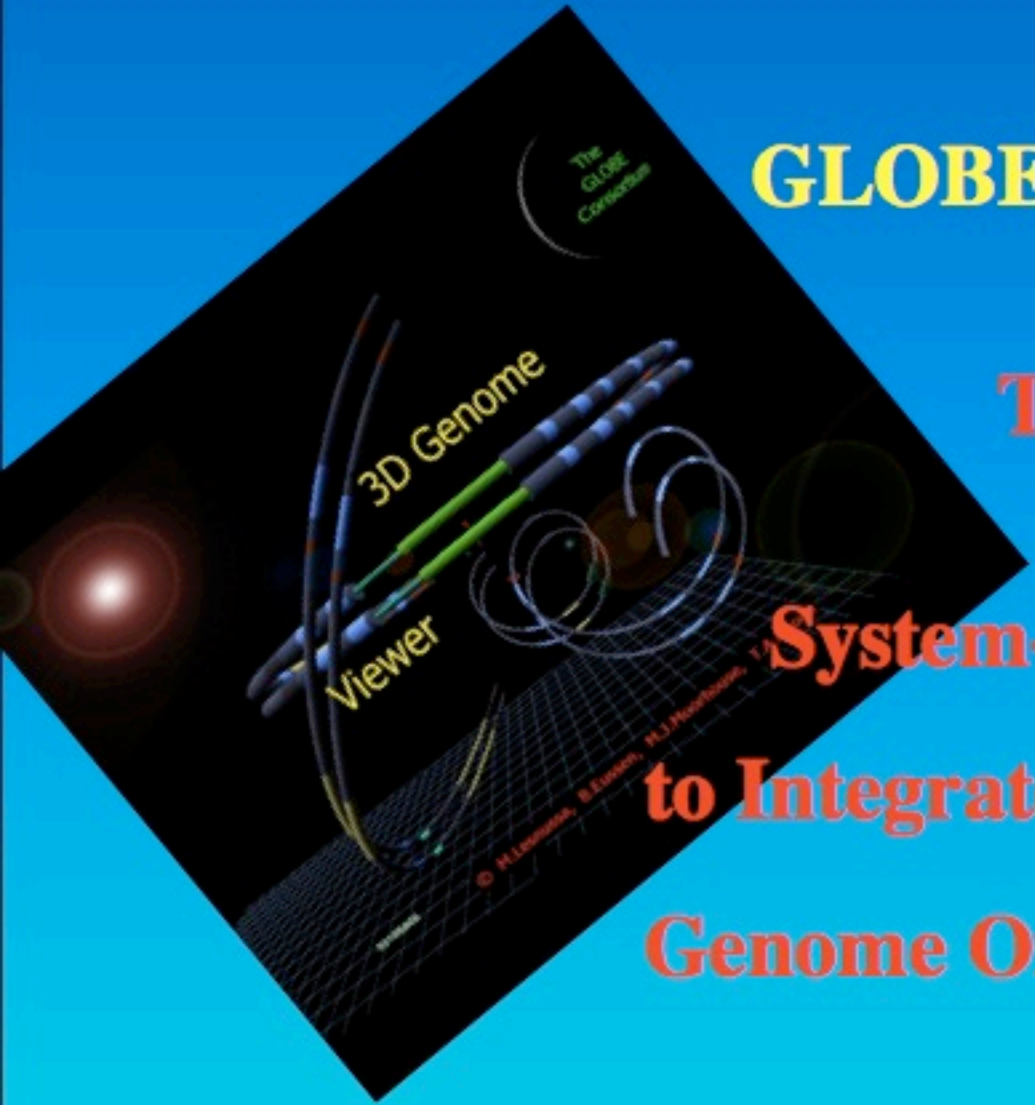

# GLOBE 3D Genome Platform

# Towards a Novel System-Biological Paper Tool to Integrate the Huge Complexity of Genome Organization and Function

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für Bildung
und Forschung
Heidelberg University
BioQuant
Kirchhoff-Institute for Physics
dkfz. German Cancer Research Center in the Helmholtz Association
MediGRID
Erasmus MC University Medical Center Rotterdam

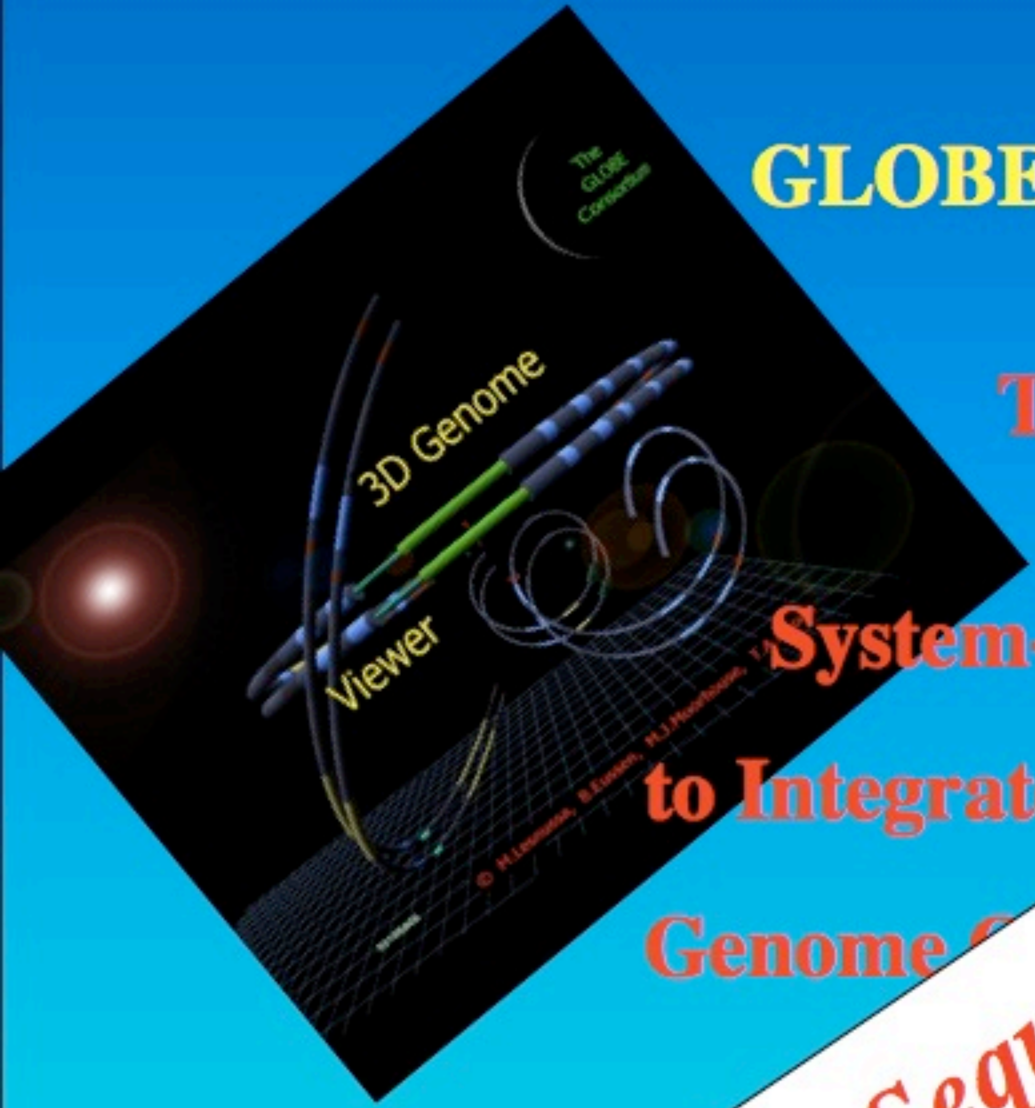
**Tobias A. Knoch, Michael Lesnussa, Nick Kepper**

**Hubert B. Eussen & Frank G. Grosveld**

**Biophysical Genomics, Cell Biology & Genetics, Erasmus MC, Rotterdam, The Netherlands**

**Biophysical Genomics, Genome Organization & Function,**
**BioQuant Cente / German Cancer Research Center (DKFZ), Heidelberg, Germany**

**Contact: TA.Knoch@taknoch.org**



Bundesministerium
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und Forschung

Heidelberg
University

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LMHOLTZ ASSOCIATION

Erasmus MC
University Medical Center Rotterdam

# GLOBE 3D Genome Platform

## Towards a Novel

## System-Biological

## to Integrate the ity of

## Genome nd Function

## From Sequence to Morphology:
## Towards a Holistic Understanding of Genomes!

**chael Lesnussa, Nick Kepper**

**. Eussen & Frank G. Grosveld**

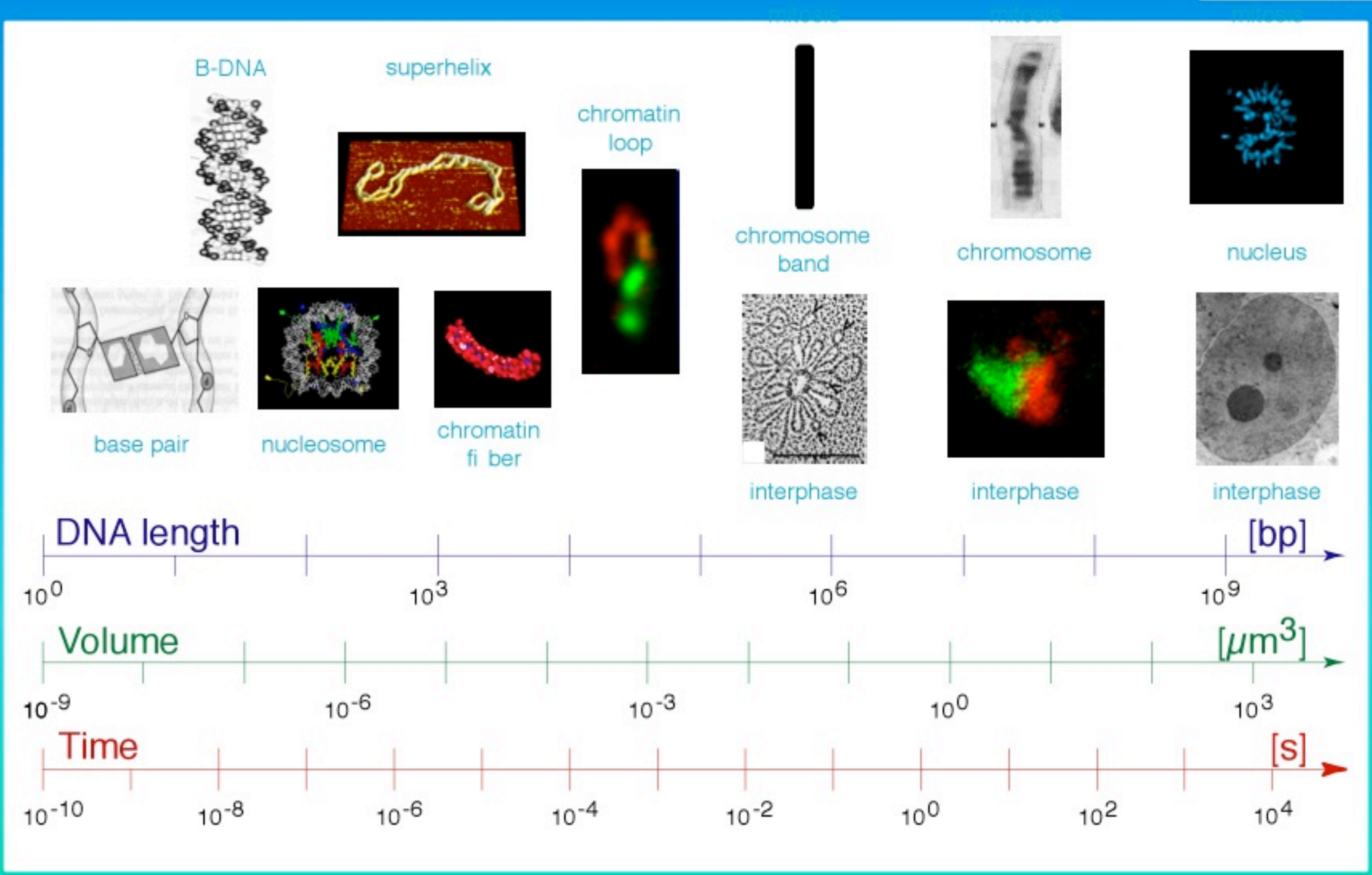
s, Cell Biology & Genetics, Erasmus MC, Rotterdam, The Netherlands

Biophysical Genomics, Genome Organization & Function,
Quant Cente / German Cancer Research Center (DKFZ), Heidelberg, Germany

Contact: TA.Knoch@taknoch.org

# Dynamic and Hierarchical Genome Organization

**The different organization levels of genomes bridge several orders of magnitude concerning space and time. How all of these organization levels connect to processes like gene regulation, replication, embryogeneses, or cancer development is still unclear?**



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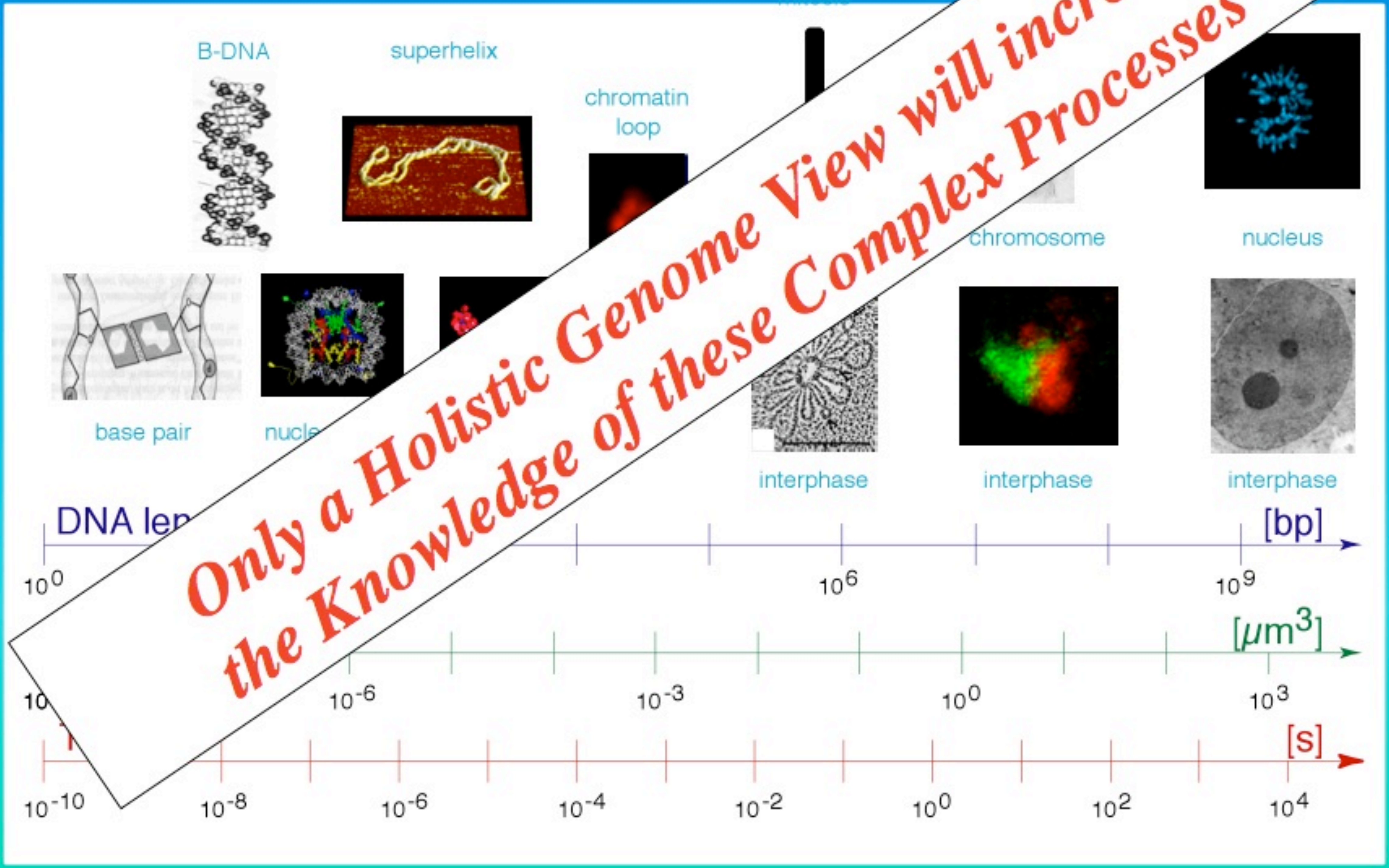


*Only a Holistic Genome View will increase the Knowledge of these Complex Processes*

# The Complexity of Cytogenetic Diagnostics

**The process of cytogenetic analysis requires proper patient and sample analysis as well asa comprehensive evaluation of the results.**

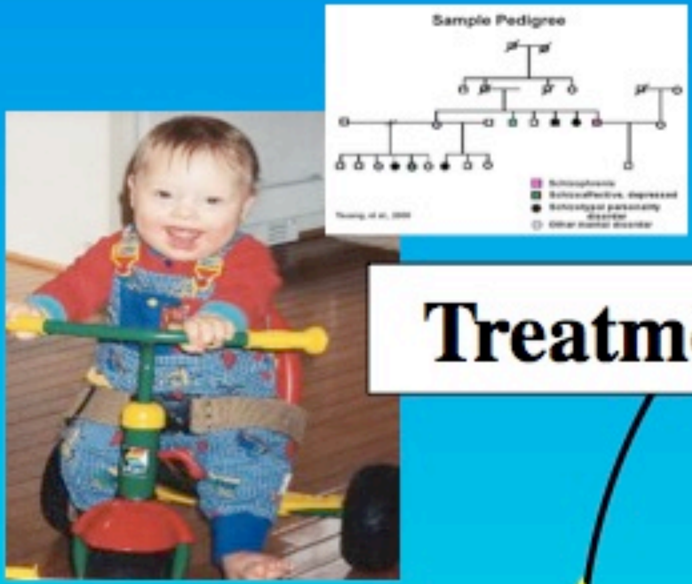
**Patient**

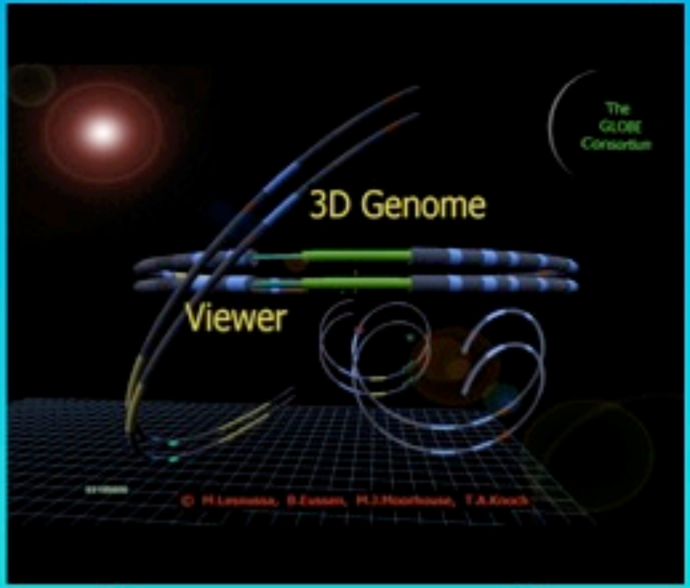
**Sample**

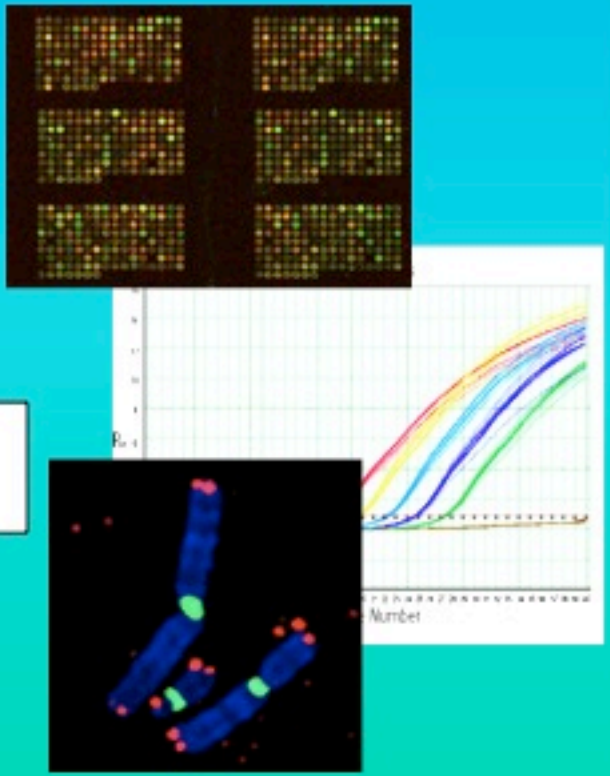
**Analysis**

**Diagnosis**

**Treatment**







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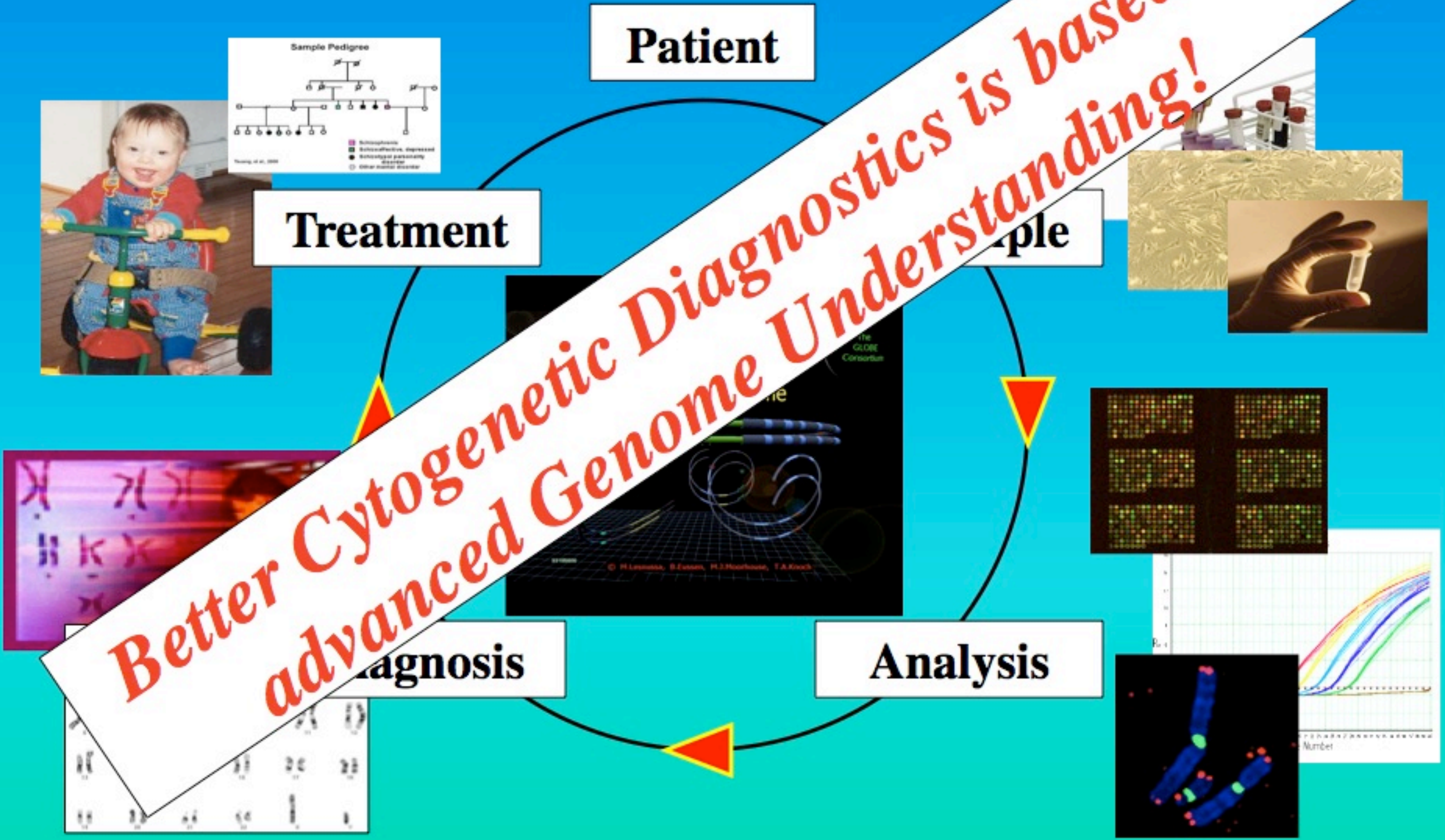


**Patient**

**ple**

**Analysis**

**agnosis**

**Treatment**

**Better Cytogenetic Diagnostics is based on advanced Genome Understanding!**

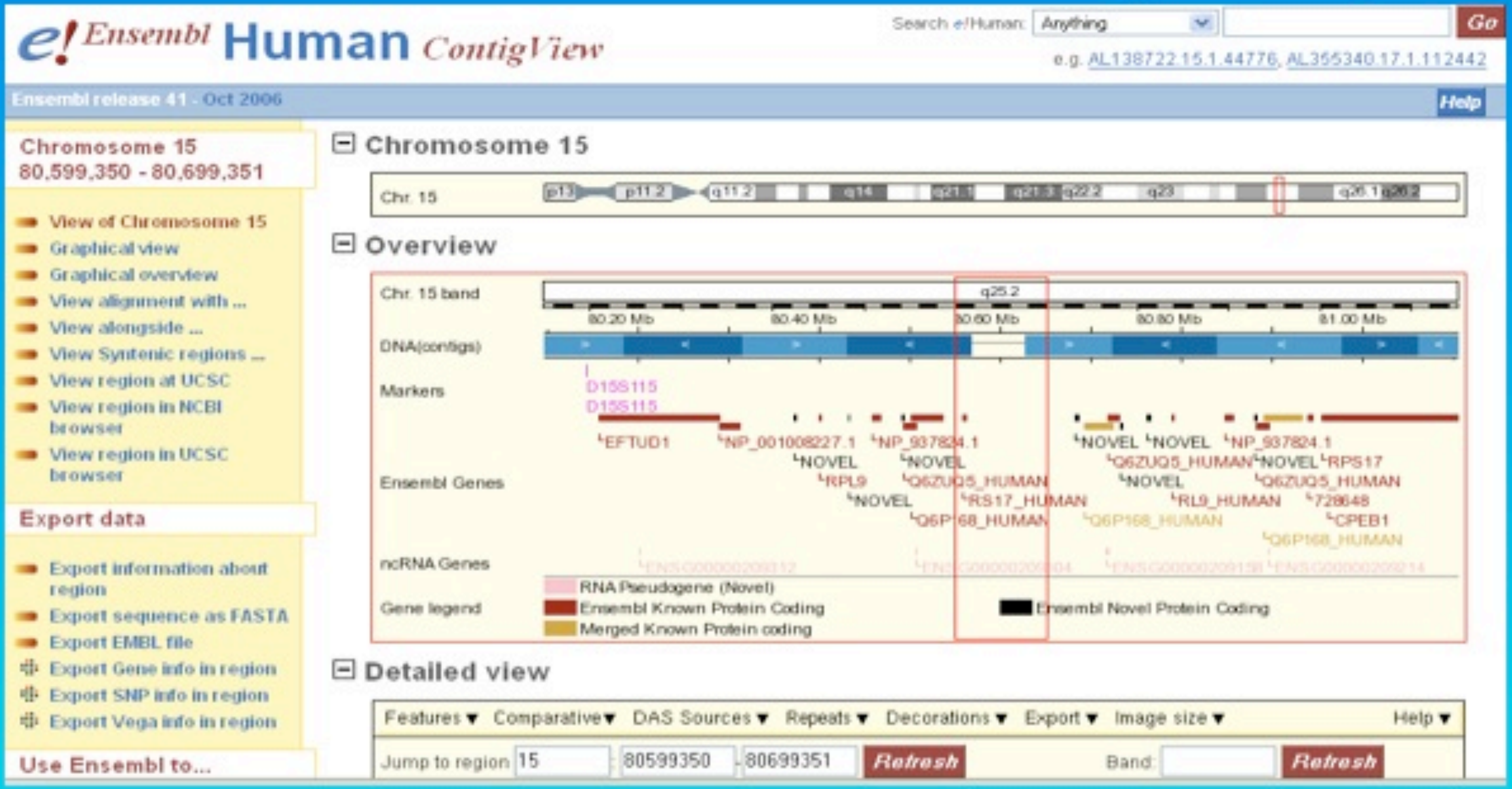
# Current 'Best of Breed'

**Current solutions are driven by the needs of specific users and data, i.e. they run on a limited paradigm with mostly fixed content, difficult user and data handling possibilities and almost no control options over processes. Thus, they neither represent adequately the complexity of genomes nor the complexity of science and industry processes necessary to work properly.**

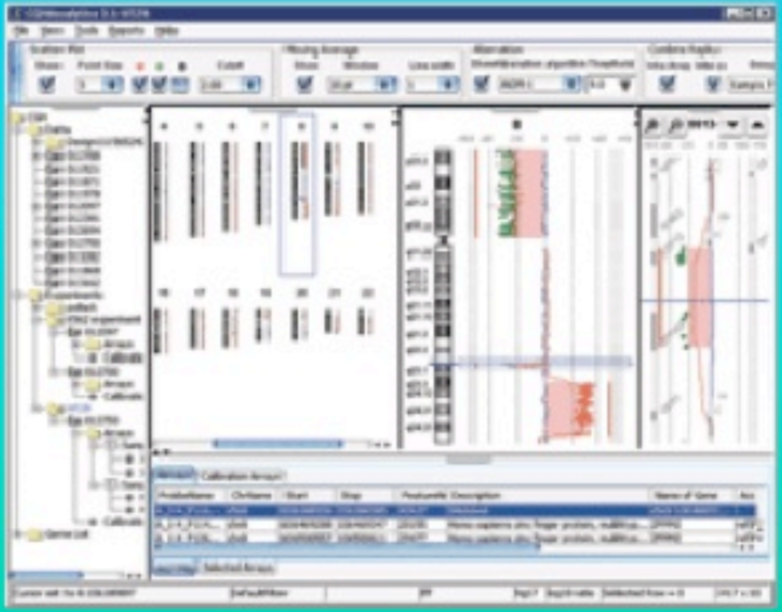
## Ensembl Genome Browser

(Open source; EBI / Sanger Center)

- fixed paradigm
- fixed content
- difficult user and data handling
- no control options

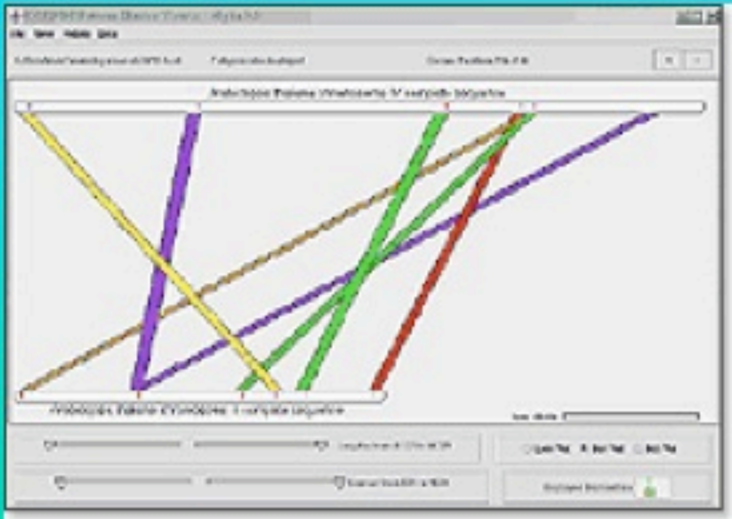


Jump to region 15 80599350 - 80699351



## CGH Analytics Software

(Agilent Inc.)



## Pattern Hunter 'Swing'

(Solutions Inc. / Sun Inc.)

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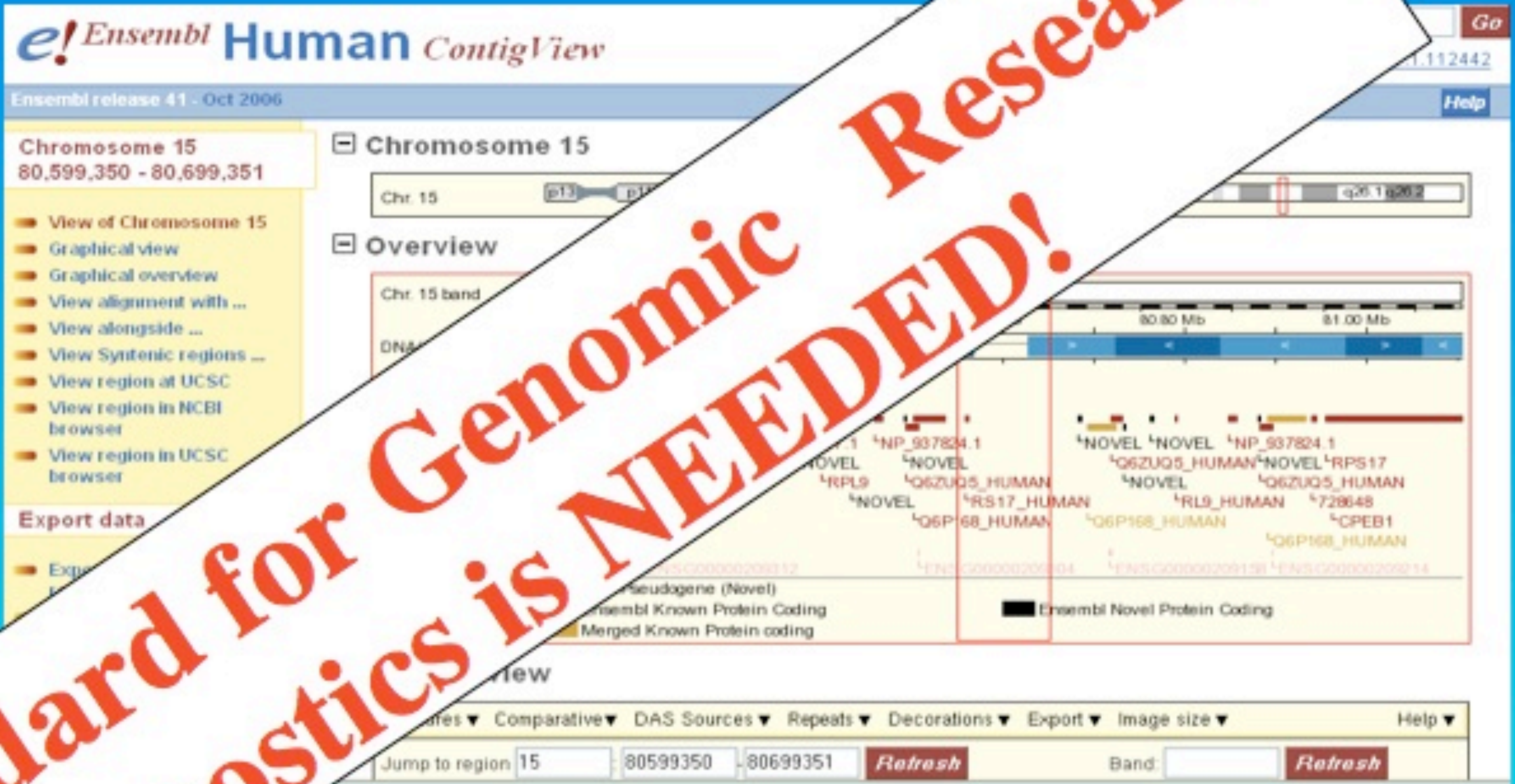

Jump to region: 15 : 80599350 - 80699351

**A NEW Standard for Genomic Research and Diagnostics is NEEDED!**

## lytics Software

**Inc.)**

## Pattern Hunter 'Swing'

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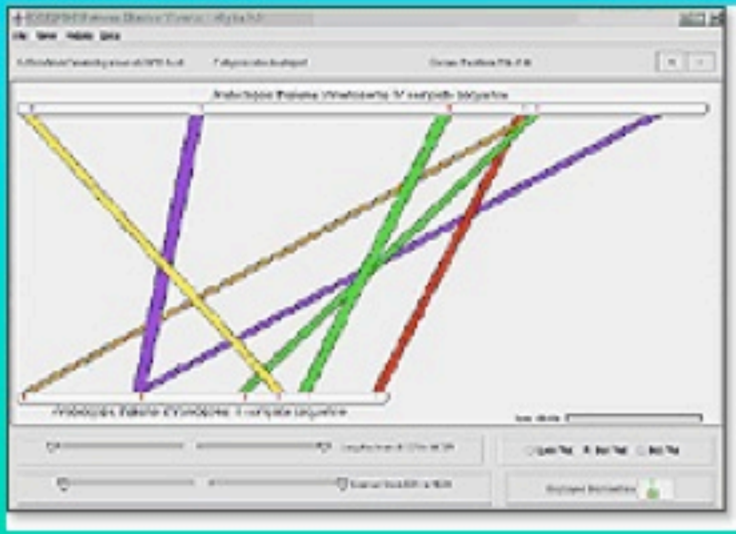

# The GLOBE 3D Genome Platform

**To develop an entire novel system-biology oriented genome browser, i.e. integrating the holistic complexity of genome organization in a single easy comprehensible platform has required completely new approaches to represent the genome architecture realistically in combination with the various types experimental data or instant analysis capabilities and annotation.**

## Paradigm:

- simplicity, flexibility, customisability, expandability and open-source sustainability

concerning

- user accessibility and needs, the in-/output of data sources, system modularity, and integration of future developments

## Content:

- all spatial scales from the base-pair to nuclear morphology including all other system composites
- every type of even large multi-dimensional datasets

## User Handling:

- intuitive navigation with dynamical semantic resolution and relational arrangement

## Data Handling:

- real-time interaction with data manipulation or annotation
- simple relational or complex correlative multi-dimensional analysis and planning capabilities

## Control Options:

- front-end access and control of virtual system biological genome simulations

# The GLOBE 3D Genome Platform

Bundesministerium für Bildung und Forschung

Heidelberg University

Kirchhoff-Institute for Physics

German Cancer Research Center

Erasmus MC

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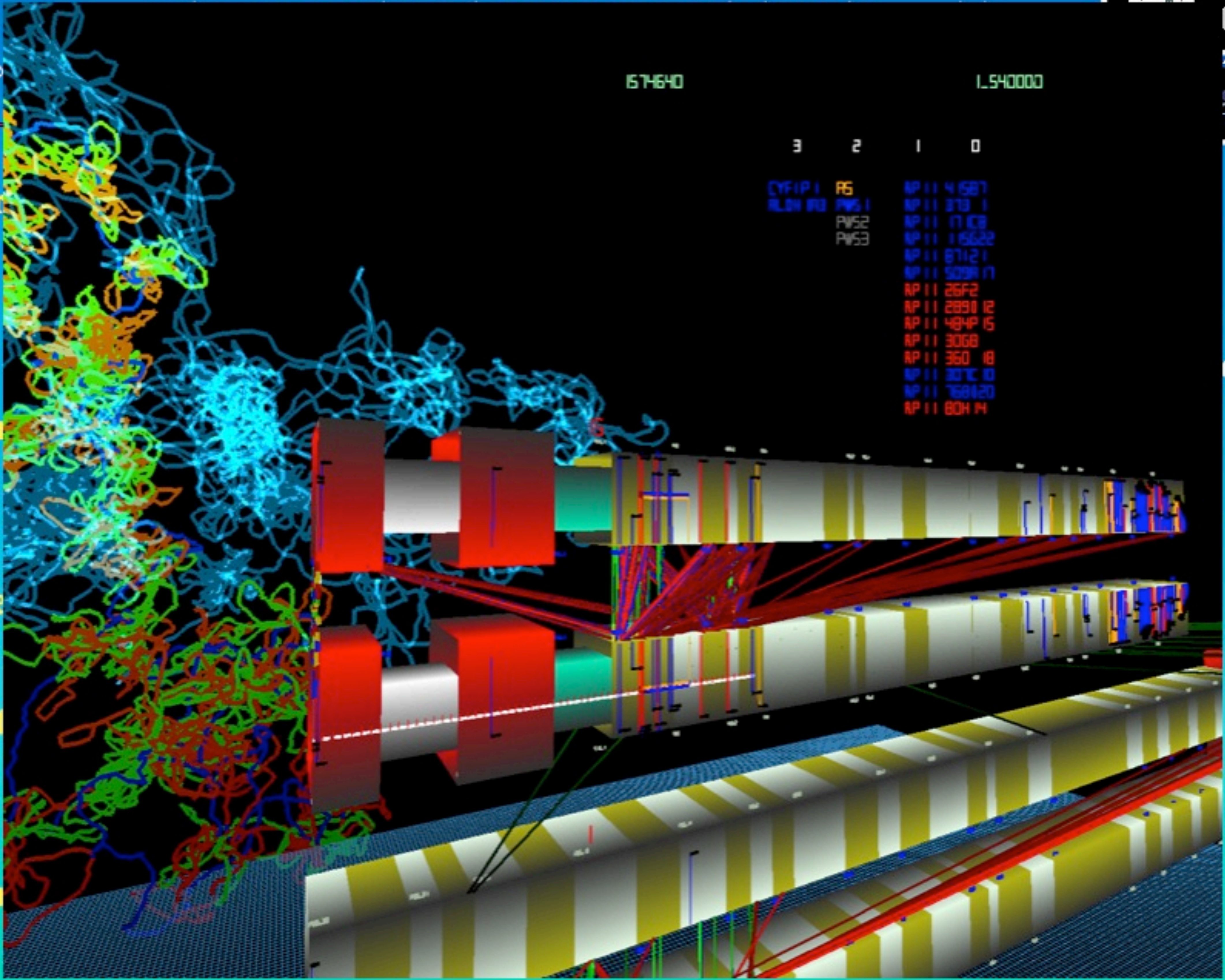

# The GLOBE 3D Genome Platform

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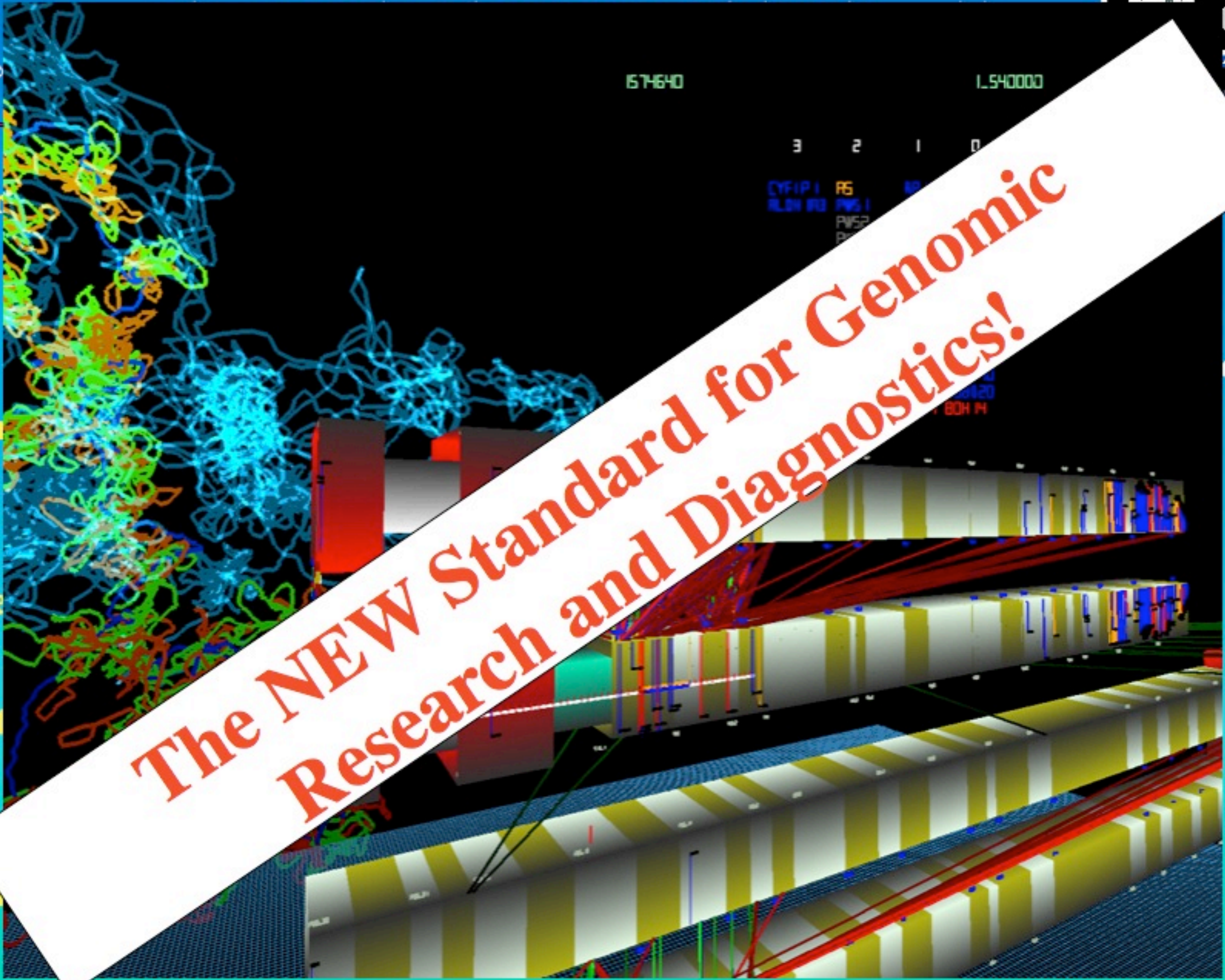

The NEW Standard for Genomic Research and Diagnostics!

# GLOBE 3D Genome Platform Visualizations

**The potential of the visualization capabilities of the platform are huge since it allows visualization of i) classical linear data, ii) correlations between data, and iii) structural data. Beyond, it allows esthetically impressive opportunities for completely new visualizations.**

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Erasmus MC

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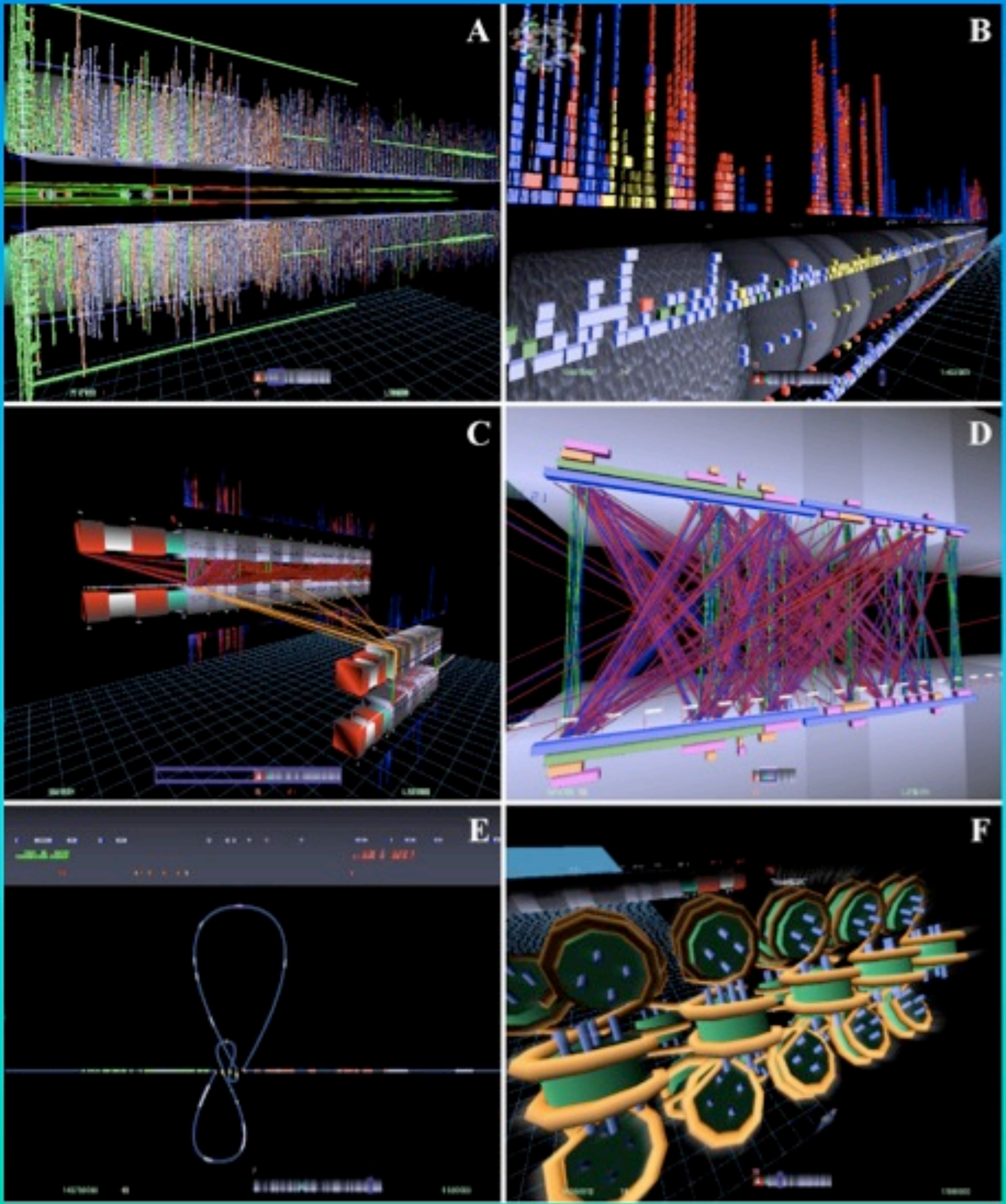

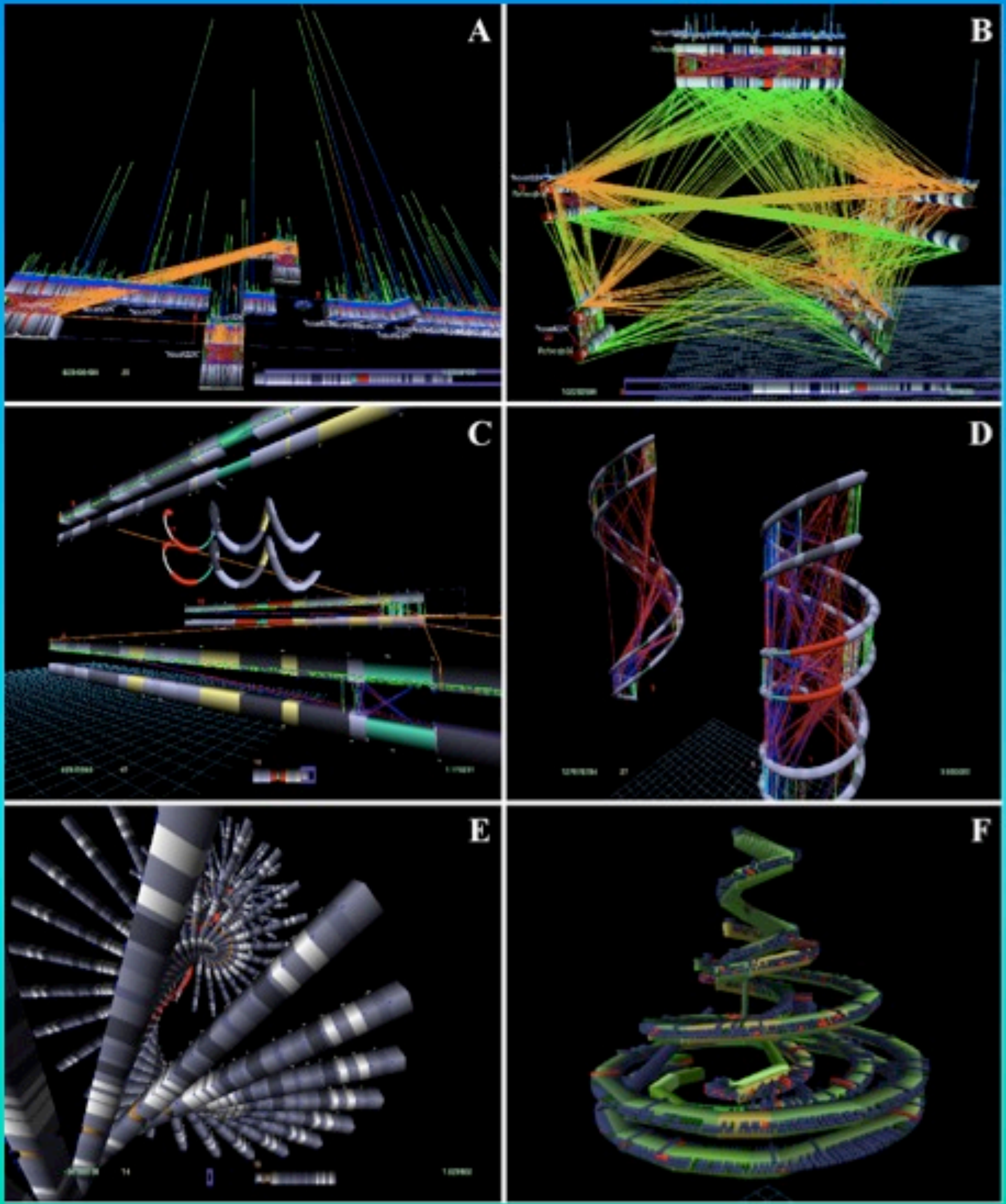

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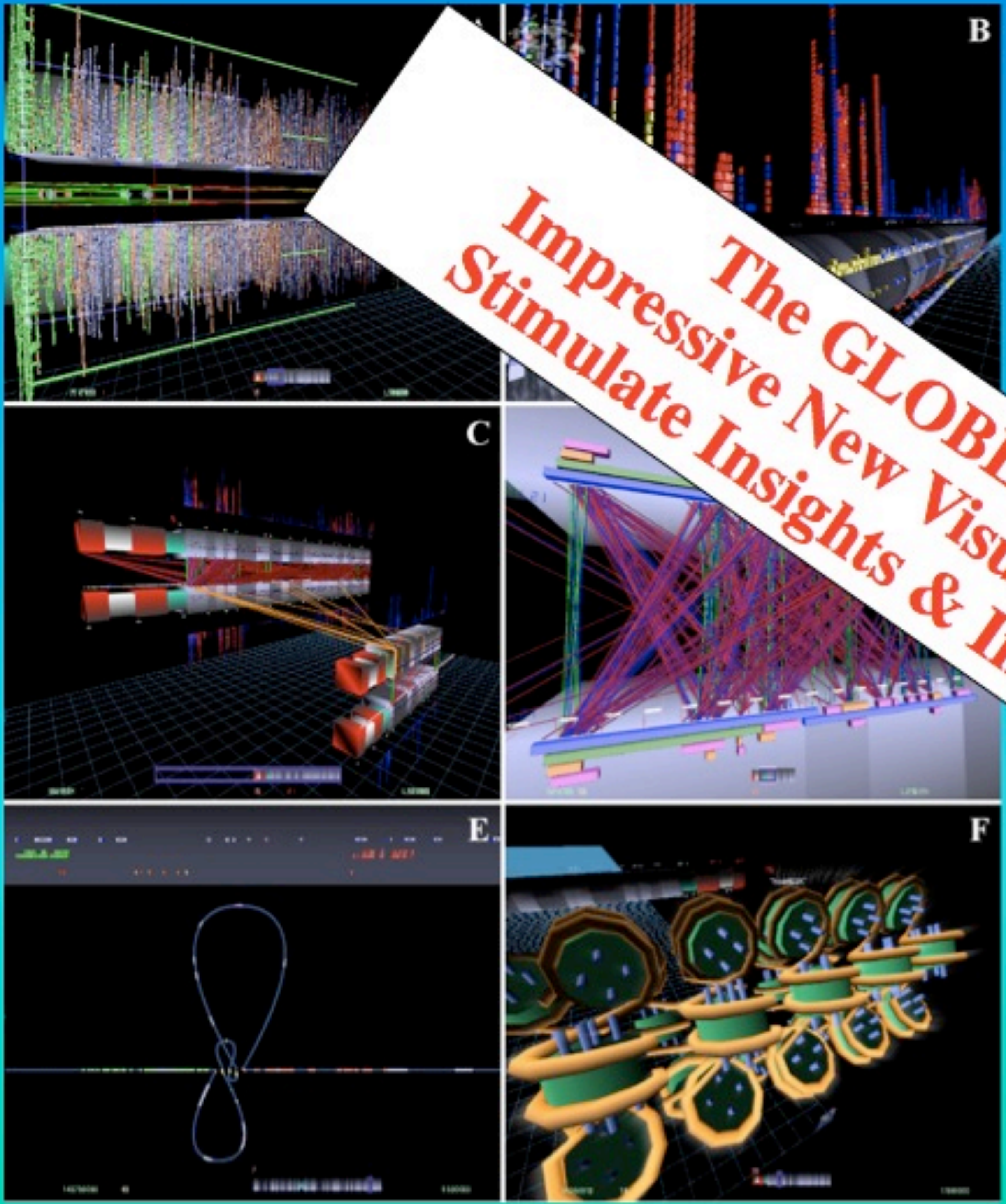

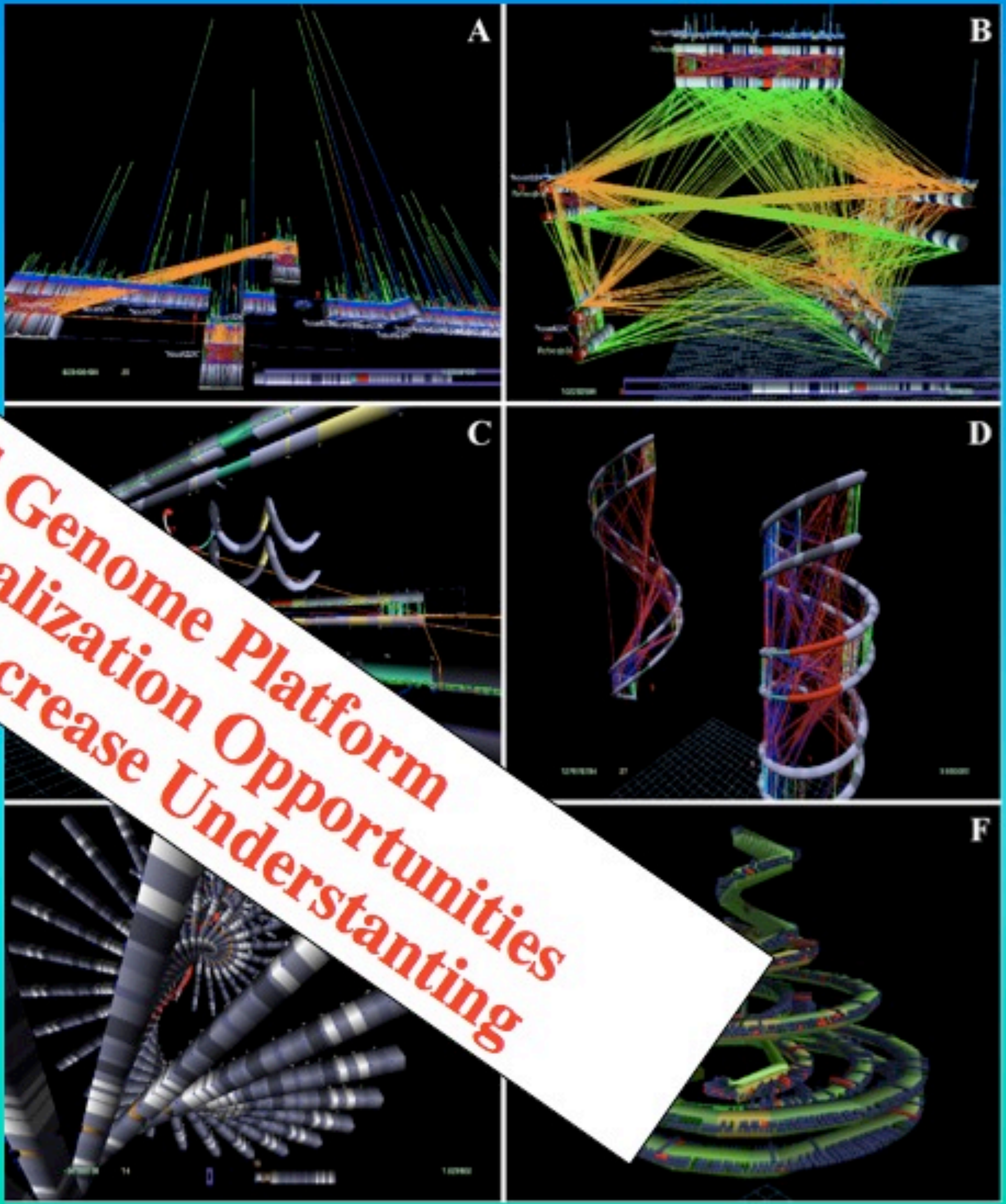

**The GLOBE Genome Platform**
**Impressive New Visualization Opportunities**
**Stimulate Insights & Increase Understanting**

# Grid-Visualization – A Novel Business Class

To enhance the performance and manageability of the platform even further, the GLOBE 3D Genome Platform is grid based, i.e. the application is running and scaling on the grid, as well as in respect to analysis on the grid and using gridded data resources. Thus, the GLOBE 3D Genome Platform represents also a new grid service and business approach / class with huge potential.

## Grid Environment:

- visualization grid clusters
- linear scaling of run-time environments
- streaming of GUI

## Computing Grid Access:

- start of analysis on grids
- management of grid workflows
- visualization of grid results

## Data Grid Access/Storage:

- grid distributed data storage/access
- access to grid data bases
- distributed working

## Manageability:

- always newest version available
- always newest liberaries and compatibilities
- always newest infrastructure available
- always user specific improvements possible
- always controlled and trusted central servicing
- always secured / trusted medical environment

## Licensing/Accounting/Prizing/Billing:

- easy licensing and user management
- accounting schemes according to usage of grid resources
- prizing schemes according to usage of grid resources
- central billing schemes

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**The Virtual Grid Desktop**

**Approaching the Ultimate Grid High-Performance Desktop Environment!**

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# The GLOBE 3D Genome Platform

**Due to its broad impact, the GLOBE 3D Genome Viewer addresses different markets and revenue streams in the areas of research, education, diagnostics and industry with different detailed business models and contracting patterns which will guaranty a constant high-profile valorization.**

## Basic Corporate License:

- 50% science
- 50% industry

## White Label Products:

- special customer products

## Content Sale

- specially defined data sets
- specially connected data sets

## Advertising:

- sponsored free version
- content and user related

## eCommerce:

- community portal and referral fees

## Companies/Organizations:

- Invitrogen (Karlsbad, CA, USA)
- Affimetrix (Santa Clara, CA, USA)
- Soft Genetics (State College, PA, USA)
- Combimatrix CMDX (San Antonio, CA, USA)
- Philips (The Netherlands)
- MediGRID (Goettingen, Germany)

## Collaborators:

- Prof. Dr. Evan E. Eichler (Seatle, WA, USA)
- Prof. Dr. Stephen W. Scherer (Toronto, Canada)
- Prof. Dr. Michael Hausmann (Heidelberg, Germany)
- Dr. Malte Wachsmuth (Seoul, Korea)
- Dr. Gregory Cox (Karlsbad, CA, USA)
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Potential costumers: 1.000.000

Revenue per customer: 1000 Euro

Market: 1.000.000.000 Euro

# The GLOBE 3D Genome Platform

## The NEW Standard for Genomic Research and Diagnostics!

## Ready to be Valorized!!!

**Basic Corporate Licenses**

**White Label Products & Advertising**

**e Commerce**

**Content Sale**

# The GLOBE 3D Genome Platform

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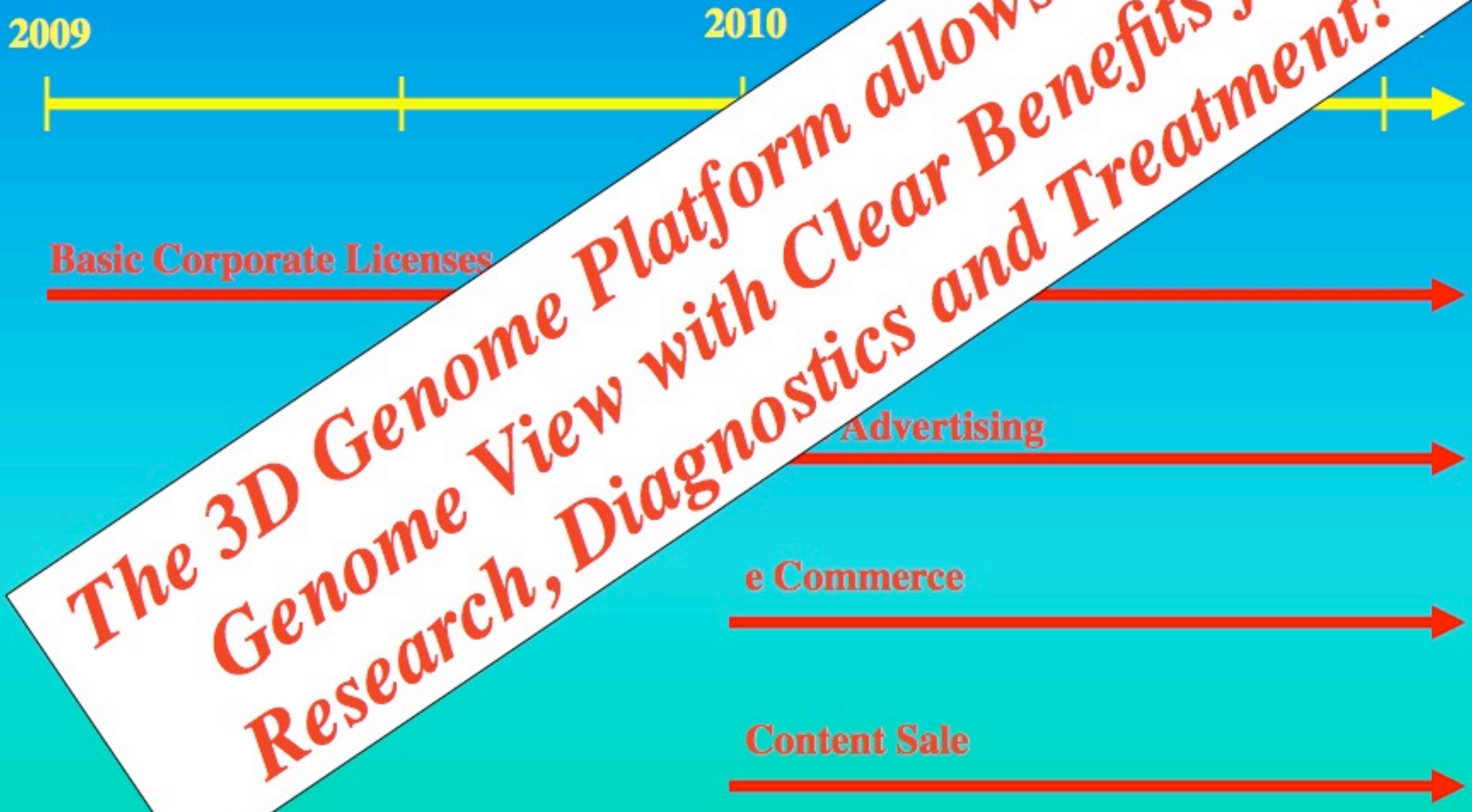

The 3D Genome Platform allows a Holistic Genome View with Clear Benefits for Research, Diagnostics and Treatment!

# The GLOBE 3D Genome Platform

-

# Towards a novel System-Biological Paper-Tool

# to integrate the

# Huge Complexity of Genome Organization and Function

**Knoch, T. A.,** Lesnussa, M., Kepper, F. N., Eussen, H. B., & Grosveld, F. G.

*HealthGRID 2009*, International Health Grid Organization, dbb Forum Berlin, Berlin, Germany, 29th June - 1st July, 2009.

## *Abstract*

The combination of genome sequence and structure, its annotation and experimental data in an accessible and comprehensible way is a major challenge. Increasingly, there are a large number of extremely divergent data sets: the sequence itself, genes, regulatory regions, various forms of reoccurring sequence features and clone sets etc. Currently, one possibility to represent this information in a visual form - and thus to reveal its scientific meaning - is to use genome browsers such as "Ensembl" or "The UCSC Genome Browser". These browsers have been beneficial in the understanding of the complex organization of genomes. However, there are also huge limitations concerning their focus on linear presentation, standardized input and data bank accessibility. Also customisability by a remote user with special requirements is difficult.

Therefore, the GLOBE-Consortium has developed the next generation genome viewer - the GLOBE 3D-Viewer - to visualize multi-dimensional data sets from various sources in an easy intuitive manor while accounting for the complexity of genome organization. Together with an easily accessible data-warehouse for archiving (un-)published experimental data and the Erasmus Computing Grid (ECG) for fast interactive large-scale (correlative) analysis the GLOBE-Consortium creates an intuitive holistic environment for genome research. Thus, the GLOBE 3D-Viewer sets the new standard to integrate complex genomic data sets within a single holistic display system and thus is major advance for scientific and clinical genome research.

### Rational behind the GLOBE 3D-Viewer

The GLOBE 3D-Viewer is based on many a basic rational driven by the complex nature of genome organization in general and by the diverse individual research and diagnostic data types in particular. Thus, the key features of the GLOBE 3D-Viewer are:

- flexibility, customisability, intuitive navigation
- real-time interaction and analysis
- dynamic scaling, semantic zooming, and object arrangement
- visualization of extremely large data sets and multi-dimensional data
- bridging all scales of genome organization from sequence to morphology

### Capabilities of the Prototype GLOBE 3D-Viewer

The GLOBE 3D-Viewer allows the integration of all possible linear and structural genomic types of information from the DNA sequence to complete genomes in a three-dimensional environment. Genomic elements are visualized in a flexible and customisable manor and can be arranged in relation to each other as desired. The navigation within this three-dimensional space is intuitive and resembles the virtual environments of flight simulators or architectural planning tools. This supports also rapid resolution change, i.e. zooming-out from the base pair to the whole-genome level is possible within an eye-glimpse using fly-in/out paradigm while including appearance or relational positioning changes of genetic elements. The GLOBE 3D-Viewer is capable of relating extremely large numbers of genomic elements and multi-dimensional data-sets to each other with inbuilt analysis running in real-time.
In addition, the GLOBE 3D-Viewer is able to present the three-dimensional organisation of genomes from base pair resolution to complete chromosomes. This allows the direct projection of linear genomic information on its real three-dimensional spatial architecture for the first time.

The GLOBE 3D-Viewer integrates e.g. the following genomic and experimental elements or data types in a three-dimensional virtual environment:

- *Genomic information types:* Syndromes, break-points, duplicons, repeat regions, epigenetic annotations, genes and single nucleotide polymorphisms.
- *Structural genome features:* Chromosomes, ideogram bands, chromatin loops, chromatin fiber conformation, nucleosomes, DNA double helix.
- *Experimental genome features:* Bacterial Artificial Chromosomes, Yeast Artificial Chromosomes, Fosmids, genomic and proteomic arrays, restricition sites, oligomers, primers.
- *Genomic experiment types:* 3D fluorescence *in-situ* hybridization (3D-FISH), Metaphase fluorescence *in-situ* hybridization (M-FISH), comparative genome hybridisation (CGH), expression profiling, quantitative polymerase chain reaction (QPCR).

The GLOBE 3D-Viewer creates entire new possibilities in the visualization in the holistic properties of genomes. It opens new perspectives for future research leading to a better understanding of genomes and their system biological aspects. This is of major importance in respect to advanced diagnostics and ultimate disease treatments.

## Opportunities of the GLOBE 3D-Viewer

The GLOBE 3D-Viewer creates a new intuitive virtual environment to show for the first the enormous complexity of genomes in a *single display*. This leads to an all encompassing understanding of genomes and opens exciting new opportunities in every aspect of scientific, clinical, education as well as commercial applications:

- *Scientists* benefit from easier planning and experimental analysis as well as hypothesis building and better comprehension of genomic function.
- *Diagnostic users* benefit from a better overview of their diagnostic tasks and the evaluation of the results including patient counselling and treatment.
- *Educators and publishers* benefit from enhanced presentation of genome organisation and function in classrooms or e-publications.
- *Commercial applicants* benefit from improved planning of new products, their in test, increased sales as well as more appealing marketing of their products.

In summary, the GLOBE 3D-Viewer offers the opportunity to understand genomes on the necessary system-biological level for the first time, and thus sets the new standard for genome browsers for scientific and clinical research and as well as for unseen possibilities concerning educational and commercial purposes. Therefore, the GLOBE 3D-Viewer creates also unrivalled chances for world-wide introduction generating a sustainable revenue stream.

*Corresponding author email contact:* TA.Knoch@taknoch.org

*Keywords:*

Genome, genomics, genome organization, genome architecture, structural sequencing, architectural sequencing, systems genomics, coevolution, holistic genetics, genome mechanics, genome function, genetics, gene regulation, replication, transcription, repair, homologous recombination, simultaneous co-transfection, cell division, mitosis, metaphase, interphase, cell nucleus, nuclear structure, nuclear organization, chromatin density distribution, nuclear morphology, chromosome territories, subchromosomal domains, chromatin loop aggregates, chromatin rosettes, chromatin loops, chromatin fibre, chromatin density, persistence length, spatial distance measurement, histones, H1.0, H2A, H2B, H3, H4, mH2A1.2, DNA sequence, complete sequenced genomes, molecular transport, obstructed diffusion, anomalous diffusion, percolation, long-range correlations, fractal analysis, scaling analysis, exact yard-stick dimension, box-counting dimension, lacunarity dimension, local nuclear dimension, nuclear diffuseness, parallel super computing, grid computing, volunteer computing, Brownian Dynamics, Monte Carlo, fluorescence in situ hybridization, confocal laser scanning microscopy, fluorescence correlation spectroscopy, super resolution microscopy, spatial precision distance microscopy, auto-fluorescent proteins, CFP, GFP, YFP, DsRed, fusion protein, in vivo labelling, information browser, visual data base access, holistic viewing system, integrative data management, extreme visualization, three-dimensional virtual environment, virtual paper tool.

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