

Tumour Cytogenetic Ring Trial 2018

Final Report Dated 19 August 2019

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Approval of Final Report:
Prof. Dr. Jürgen Kunz, BVDH e. V., Berlin

**Berufsverband Deutscher
Humangenetiker (BVDH) e.V.**

Expanded Committee for Quality Assurance

Members elected:

Prof. Dr. rer. nat. Jürgen Kunz (chairman)

Dipl.-Biol. Susanne Anders

PD Dr. rer. nat. Barbara Fritz

PD Dr. rer. nat./med. habil. Thomas Liehr

Dr. rer. nat. Anja Weise

RT supervisors:

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Dr. rer. nat. Eveline Fiedler

Prof. Dr. med. Claudia Haferlach

Sarah Matos Meder, M. Sc.

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RT Supervisors Tumour cytogenetics

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Aims of Ring Trial

- External quality assessment of “Chromosome Banding Analysis of Leukemic Cells”
- Verification of the whole analytical method and the findings reports by ring trials using vital cells
- Establishment of the comparability of the overall analytical performance between different laboratories

Method

- Vital cells
- Cell line with aberrant karyotype
- Preparation of a surrogate leukemic sample by means of a defined proportion of the cell line and blood of a healthy donor
- Express shipment
- Chromosome banding analysis according to standard work instruction of the laboratories
- Upload of the findings to assessment platform
- Evaluation of the findings by a review committee

Tasks of the Review Committee

- Definition of target aberrations
- Evaluation of the chromosome findings according to the guideline criteria

Ring Trial Supervisors

- Harald Rieder
- Karin Hardt (deputy)

Assessment Committee

- Sönke Arps
- Jutta Bradtke
- Detlef Haase
- Claudia Haferlach
- Lana Harder
- Antje-Friederike Pelz
- Gabi Prescher
- Helmut Spring
- Marc Tapp
- Friedel Wenzel

Evaluation Procedure

- Online via ring trial platform
- Two experts and one ring trial investigator each evaluate the documents of participants
- Internal coordination between the reviewer via a telephone conference at the beginning and one at the end of the assessment procedure

Surrogate Leukemic Sample

- Venous blood of a healthy female donor
- Target cell line (100%): MOLT-14
- Envisaged cell count:
 - 10 000 / μ L

Target Cell Line

- Cell line: MOLT-14
- Origin: 2-year-old girl with T-cell acute lymphoblastic leukemia, established from relapse in 1983
- Immunophenotype: CD3 +, CD5 +, CD7 +, CD8 -, CD13 -, CD19 -, TCRalpha/beta -, TCRgamma/delta +
- Karyotype (according to description): 46(44-48)<2n>XX, der(17)t(17;17)(p13;q22.1)



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Ring Trial Tumour cytogenetics 2018

Delivery note

Sender Prof. Dr. Harald Rieder
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**Patient
born** Molly Torteen (female)
03 Oct. 2014

Diagnosis: Acute lymphoblastic Leukemia
Therapy: None

Blutbild: Leukocytes 10.000/ μ l
Approximately 50% blasts

Material: Approximately 1.5 ml peripheral blood, heparinised
(10 i.U. Lithium-Heparin/ml)

Sample taken 16 Oct. 2018

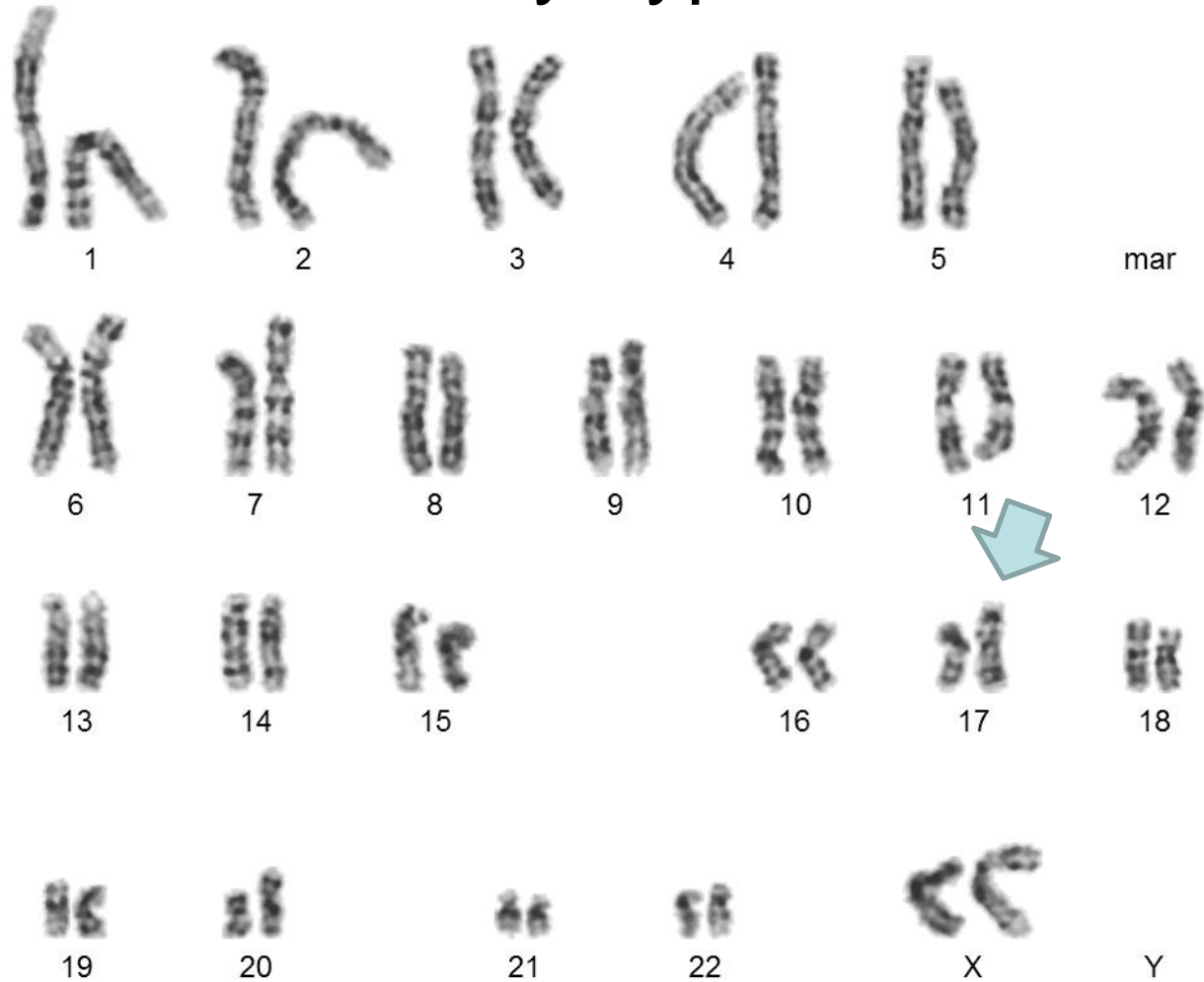
Remit:
Analysis of chromosomal banding (Quality assurance, no reimbursement of costs!).
Date: 16 Oct. 2018



Prof. Dr. Harald Rieder

Further information can be found on the ring trial's web page:
<http://www.bvdh-ringversuche.de>

Karyotype



Definition of Target Aberrations

(telephone conference 27 Nov 2018)

The following target aberrations were unanimously defined:

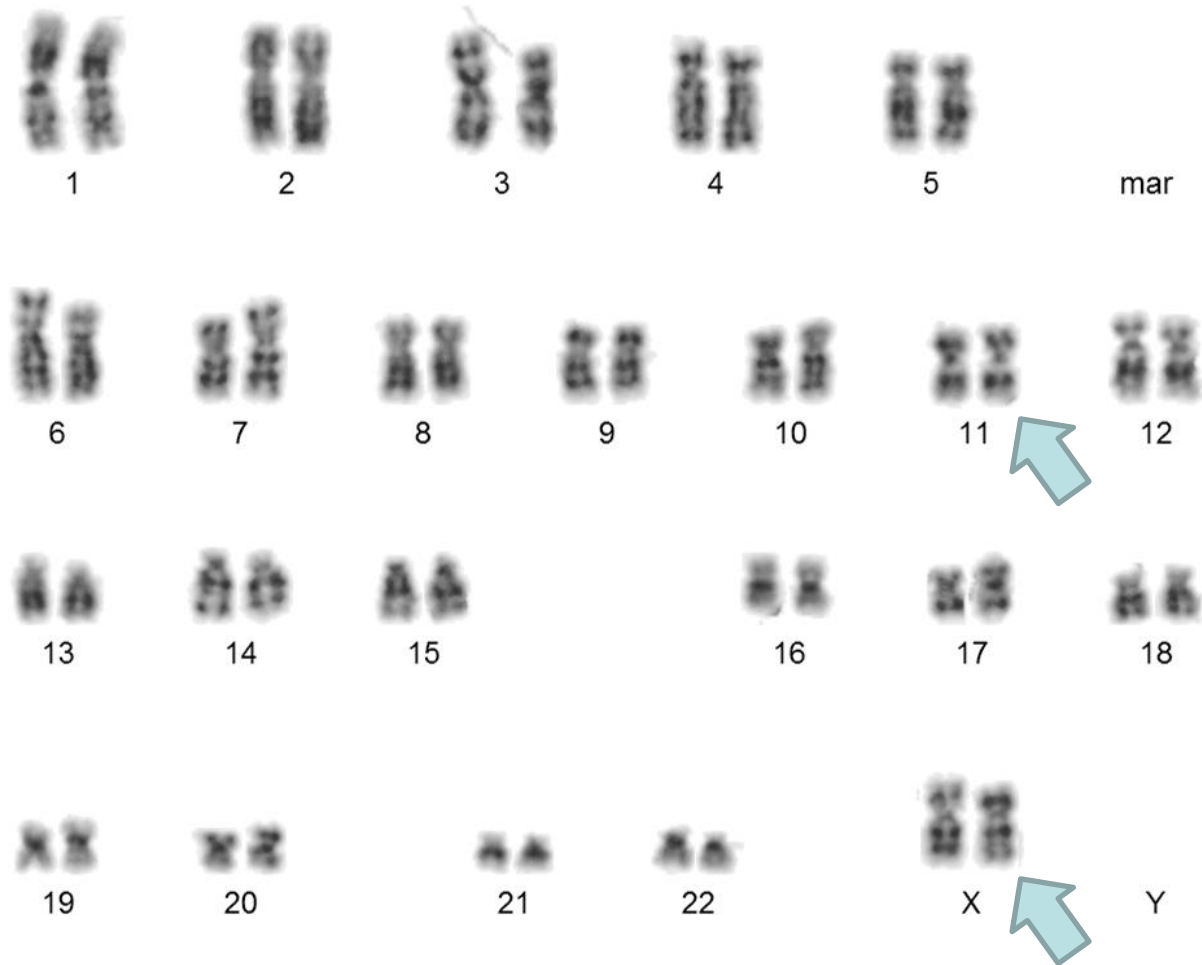
Target aberration 1:

$\text{add}(17)(p?)/\text{der}(17)\text{t}(17;17)(p13;q22)$

Comment: reliably detectable in all metaphase cells



Karyotype

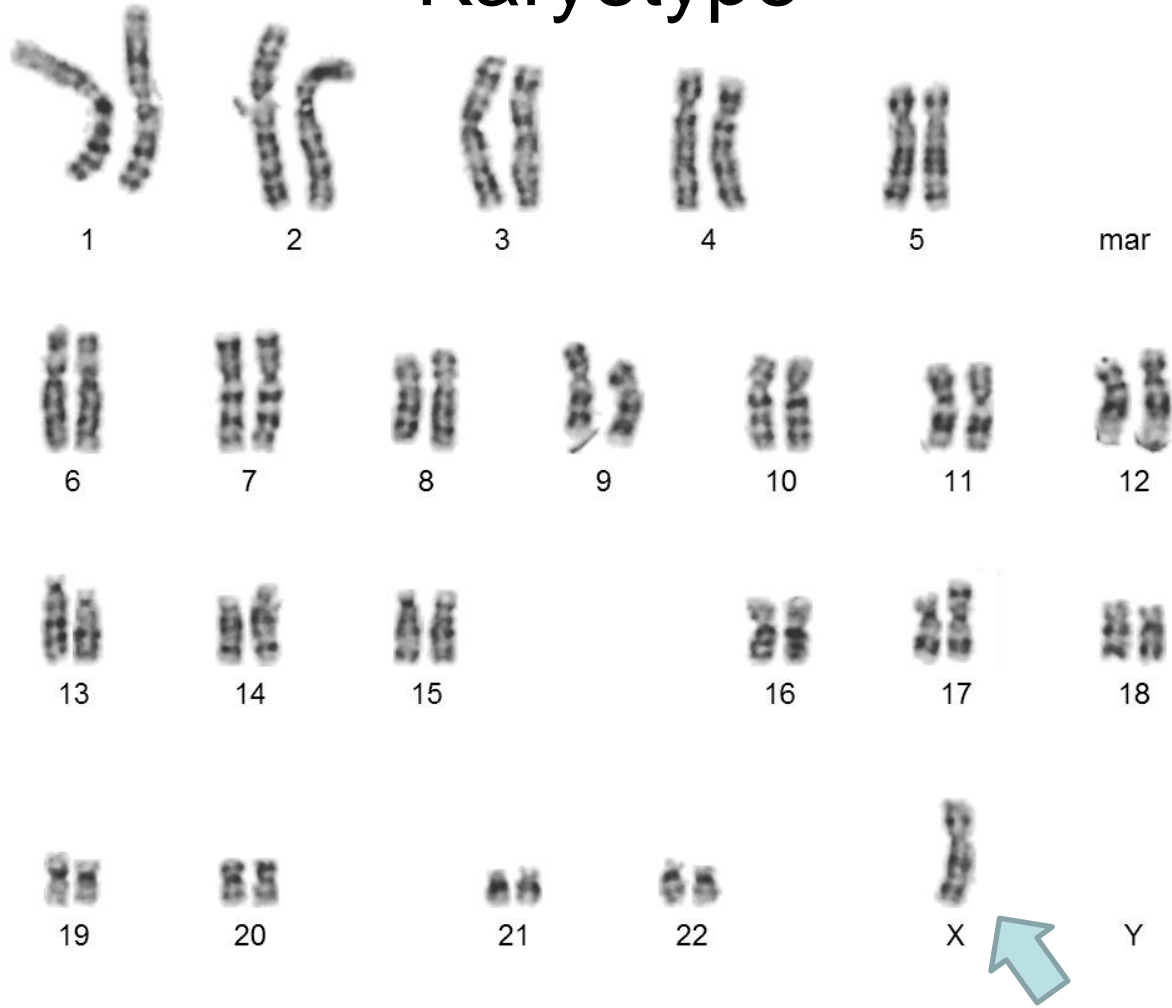


Definition of Target Aberrations

(telephone conference 27 Nov 2018)

- The following target aberrations were unanimously defined:
- Target aberration 1:
 - $\text{add}(17)(p?)/\text{der}(17)\text{t}(17;17)(p13;q22)$
 - Comment: reliably detectable in all metaphase cells
- Target aberration 2:
 - $\text{add}(11)(p?)/\text{t}(X;11)(q25;p13\sim15)$
 - Comment: not reliably detectable in all metaphase cells

Karyotype



Definition of Target Aberrations

(telephone conference 27 Nov 2018)

The following target aberrations were unanimously defined:

- Target aberration 1:
add(17)(p?)/der(17)t(17;17)(p13;q22)
Comment: reliably detectable in all metaphase cells
- Target aberration 2:
add(11)(p?)/t(X;11)(q25;p13~15)
Comment: not reliably detectable in all metaphase cells
- Target aberration 3:
-X
Comment: not reliably detectable in all metaphase cells, rather small clone

Review of Definition of Target Aberrations

(telephone conference 24 Feb 2019, following first assessment)

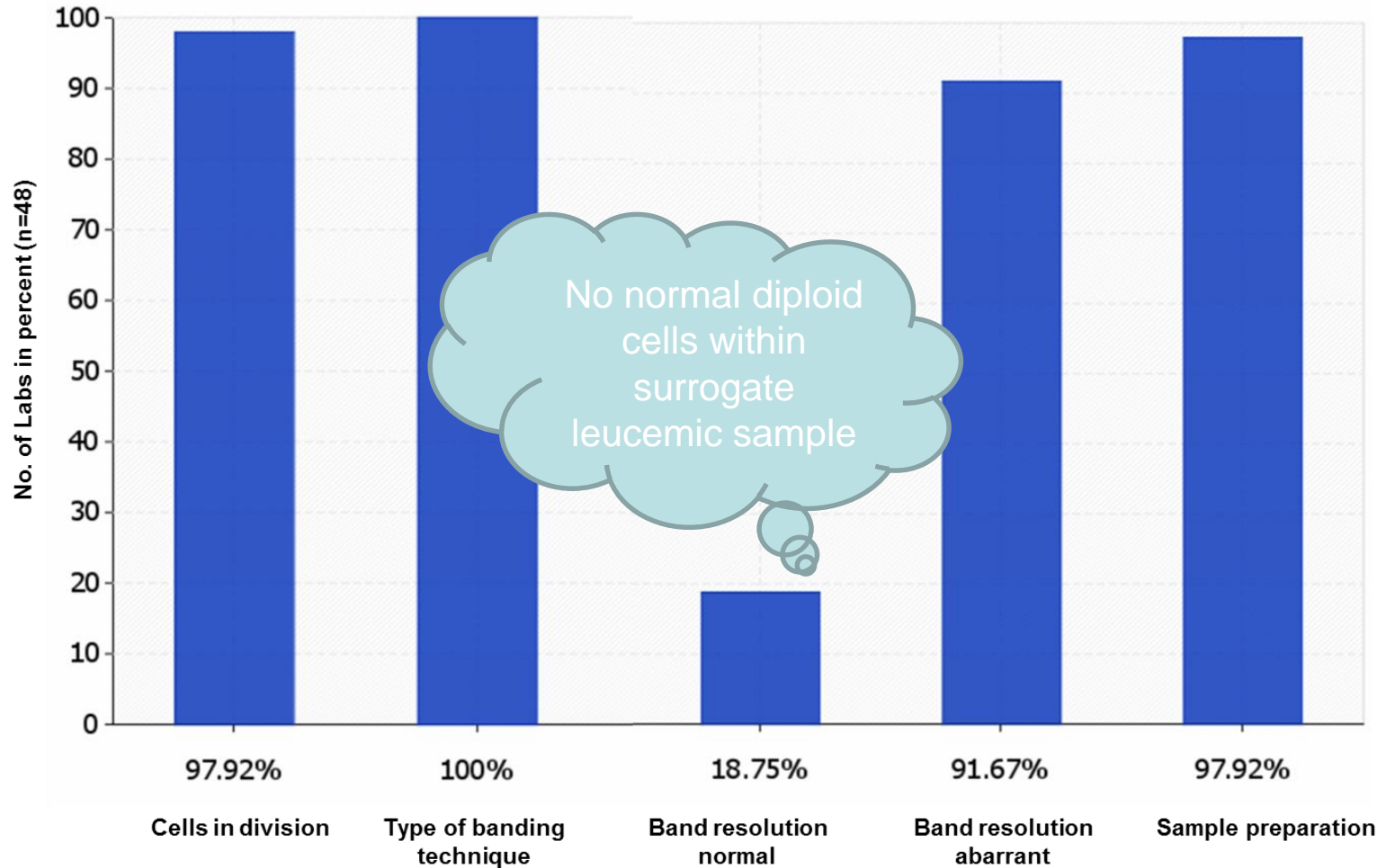
- Only 7 laboratories had found the target aberration 3 (-X). Therefore, this target aberration is not considered in the assessment of the ring trial.
- The experts agreed that reference to the aberrated chromosome 17 as an isochromosome with and without additional structural changes is inadmissible.

Tumor Cytogenetic Ring Trial 2018

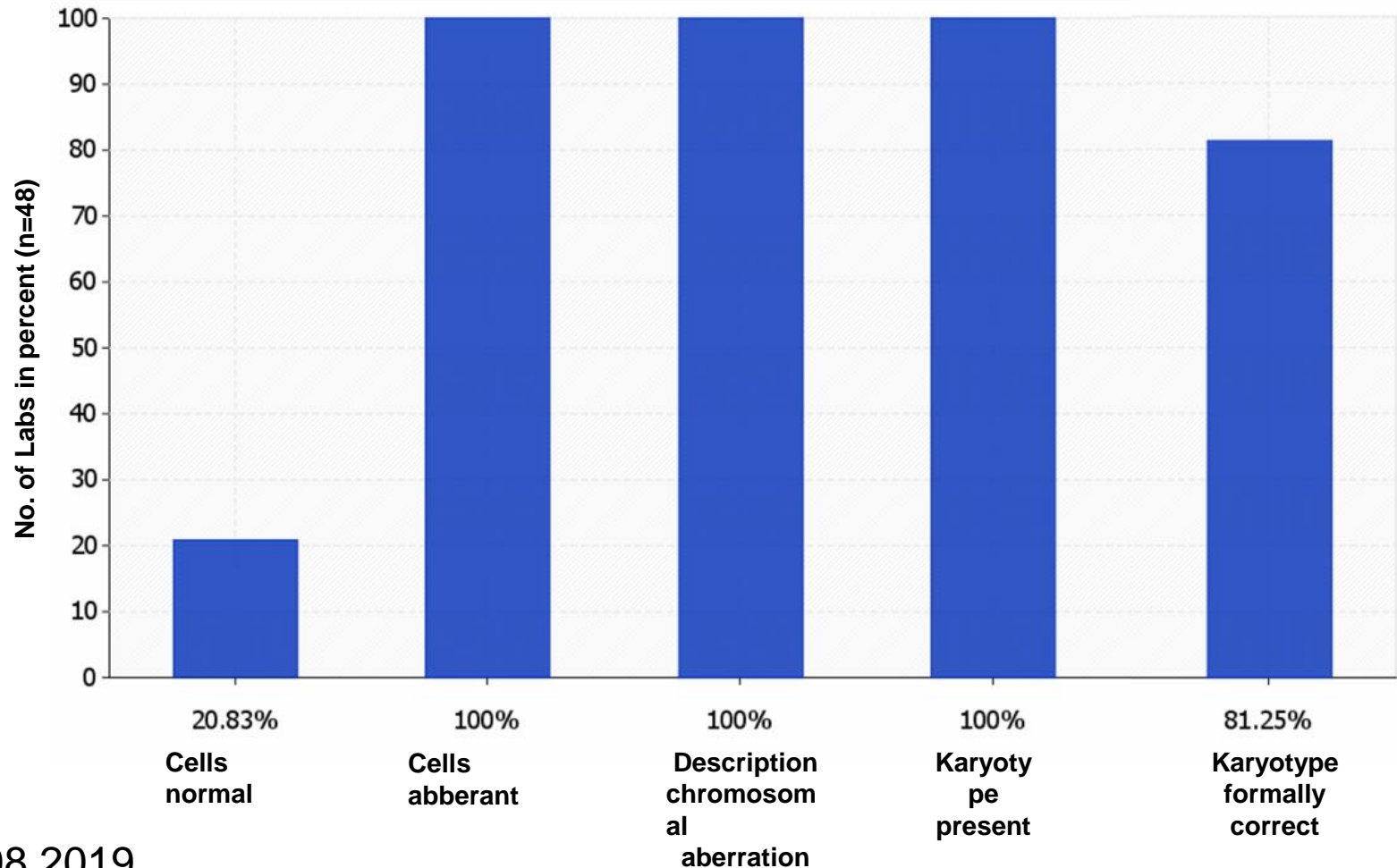
RESULTS



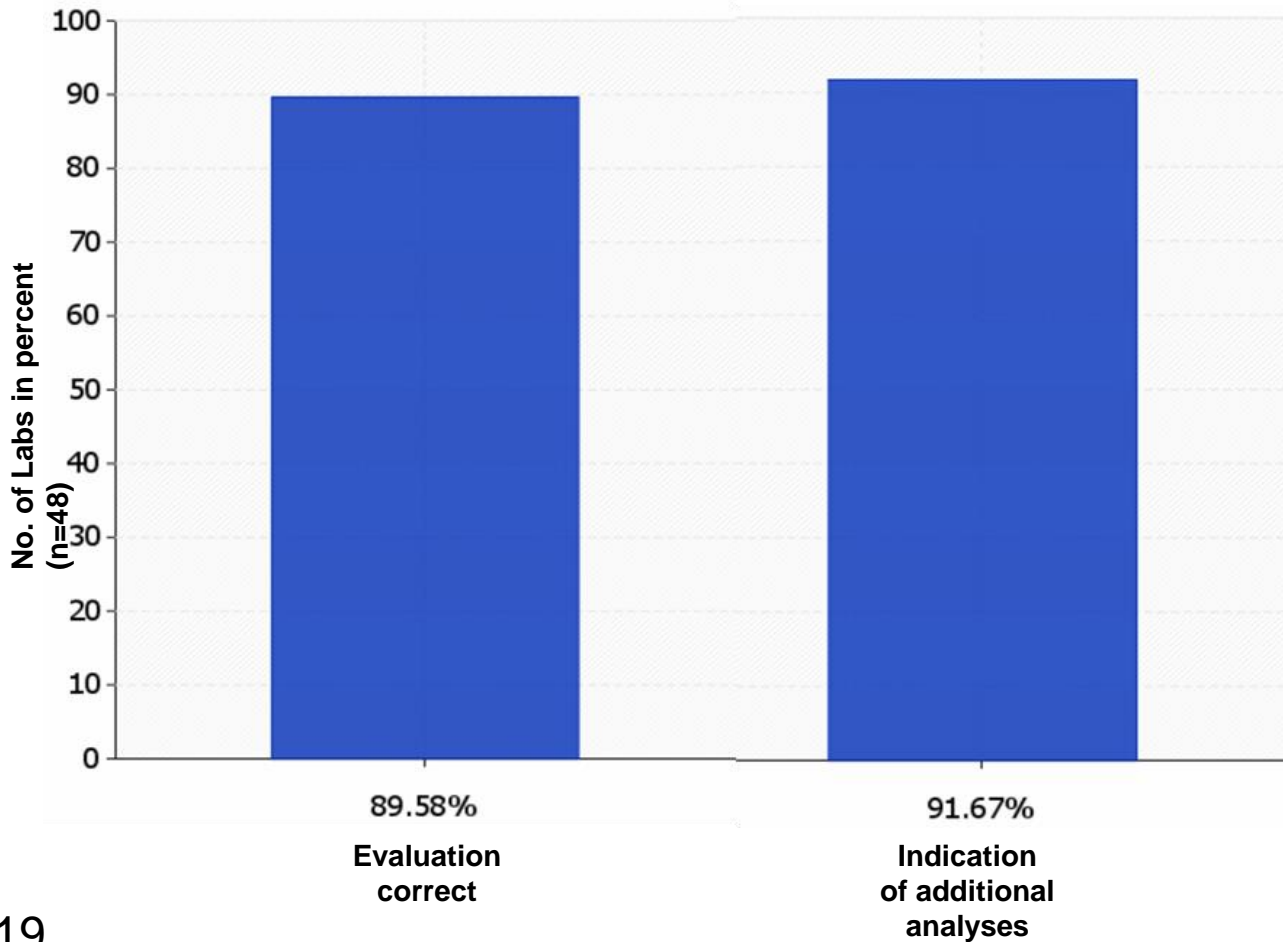
Details Regarding Test Method



Details Regarding Cytogenetic Result



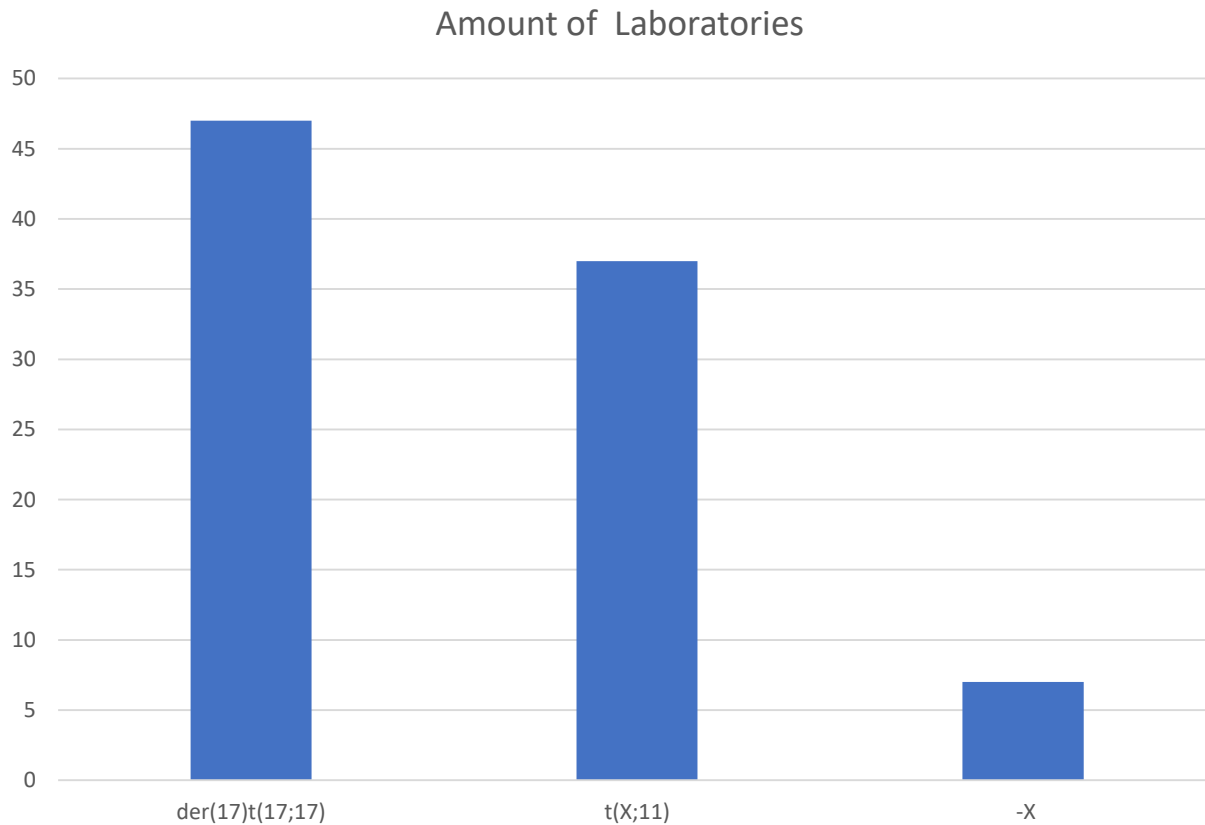
Evaluation



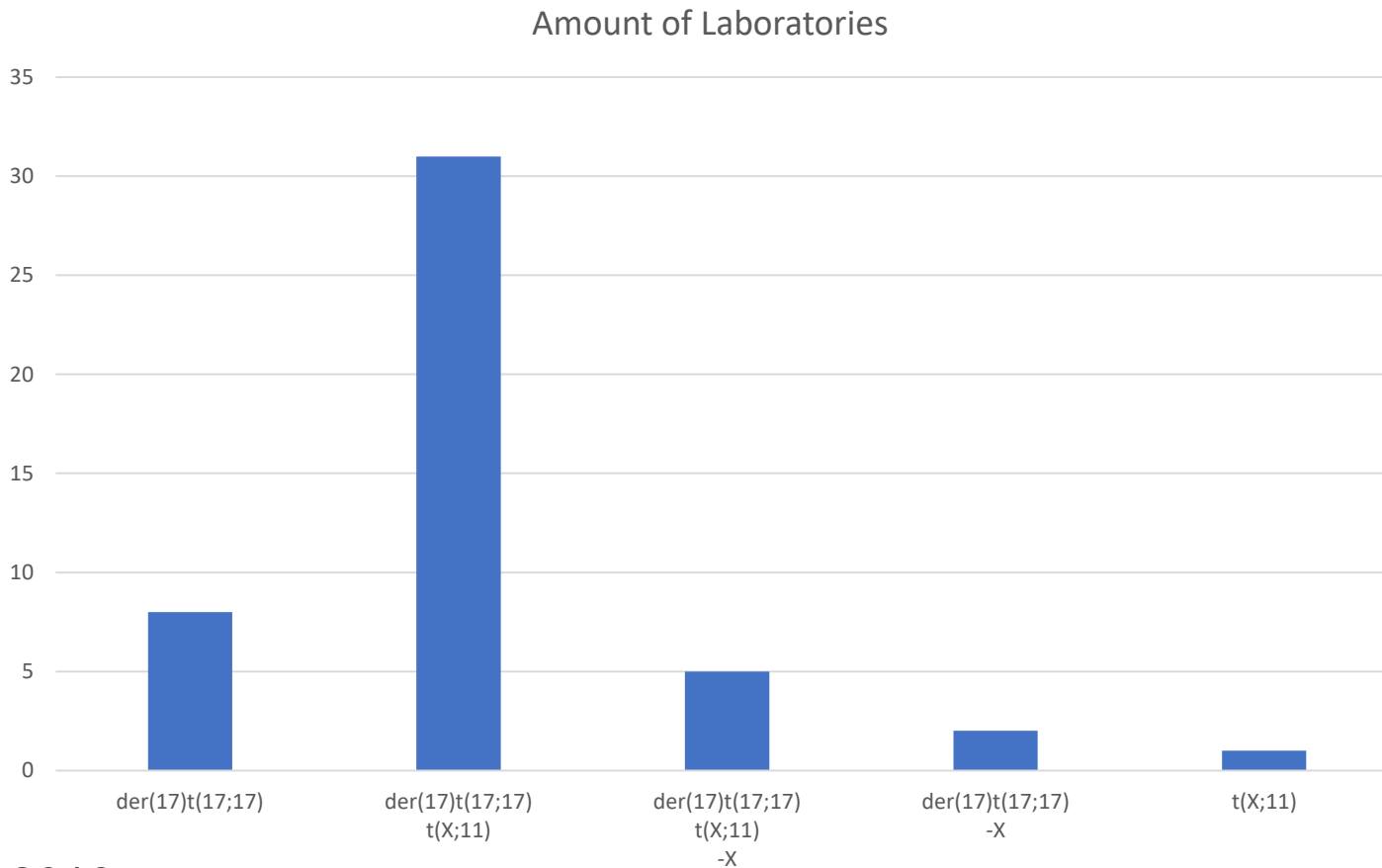
Target Aberrations



Frequency of Target Aberrations



Combinations of Target Aberrations



Karyotype Errors



Incorrect Description of t(X;11) (n=4)

Karyotype according to ISCN 2016:

46,XX,t(X;11)(q25;p13),der(17)t(17;17)(p13;q22)[30]/46,XX[17]

- The modal chromosome number of 46 does not match the further karyotype description since the description provided of the translocation with the involvement of an X chromosome with the simultaneous indication of two inconspicuous chromosomes presupposes a supernumerary X chromosome. This would be possible, for instance, with a 47,XXX karyotype. The actual chromosome finding regarding the gonosomes is correctly described with 46,X,t(X;11).

Interpretation Errors



What are interpretation errors?

- A chromosome abnormality is found and wrongly interpreted as a typical chromosomal aberration (e.g. $\text{inv}(16)(\text{p}13\text{q}22)$ for overlarge heterochromatin).
- An obvious chromosome aberration is overinterpreted regarding its relevance (e.g. loss of a single chromosome as an indication of a low-hypodiploid karyotype, several chromosome aberrations as a complex aberrant karyotype).

Critical Misinterpretations

- Misinterpretation of a chromosome aberration
- Wrong conclusions
- Misinformation to the attending physician with potentially negative impact on the treatment of the patient

Decision of Review Committee

- Introduction of the parameter “Critical misinterpretation of findings” from the next ring trial

Introduction of a passing criterion for accreditation is required.

Proof of a target aberration is required from the next ring trial which is pre-defined by the Expert Commission and can be reliably verified.

Summary

- Detection of the target cell line by all laboratories
- Detection of target aberration 1 by almost all laboratories
- Correct assessment of the chromosome finding in 90% of the cases
- Correct karyotype description according to ISCN in more than 80% of the cases
- Largely a problem with the description of gonosomal structural aberrations
- New considerations for assessment from the next ring trial:
 - Introduction of the parameter “Critical misinterpretation of findings”
 - Introduction of a passing criterion in the form of detection of a defined target aberration

Complaints / Objections

- You can lodge a complaint about this trial in general or object against your individual evaluation
- The objection or complaint must be sent in text form to the Coordination Office.
- Deadline for complaints/objections: 17 September 2019

[End of Final Report]