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Clinical use of SNP-microarrays for the detection of genome-wide changes in haematological malignancies

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ABSTRACT

Single nucleotide polymorphism (SNP) microarrays are commonly used for the clinical investigation of constitutional genomic disorders; however, their adoption for investigating somatic changes is being recognised. With increasing importance being placed on defining the cancer genome, a shift in technology is imperative at a clinical level. Microarray platforms have the potential to become frontline testing, replacing or complementing standard investigations such as FISH or karyotype. This 'molecular karyotype approach' exemplified by SNP-microarrays has distinct advantages in the investigation of several haematological malignancies.

A growing body of literature, including guidelines, has shown support for the use of SNP-microarrays in the clinical laboratory to aid in a more accurate definition of the cancer genome. Understanding the benefits of this technology along with discussing the barriers to its implementation is necessary for the development and incorporation of SNP-microarrays in a clinical laboratory for the investigation of haematological malignancies.

1. Introduction

We are in an era of rapid change in diagnostic genomic testing methods used to detect somatic genome-wide alterations for haematological malignancies. This has concurrently resulted in the discovery of rare or novel changes, the identification of new subtypes of established haematological malignancies such as BCR-ABL1-like acute lymphoblastic leukaemia (ALL) (Arber, Orazi et al. 2016). SNP-microarrays have emerged as a powerful tool for the detection of genome wide genetic changes with prognostic and/or predictive value (Simons, Sikkema-Raddatz et al., 2012; Genetics and Genomics Laboratory Quality Assurance, 2013; Kloosterman and Cuppen, 2013; Xu, Johnson et al., 2013; Medeiros, Othus et al., 2014; Paskulin, Giacomazzi et al., 2014; Renneville, Abdelali et al., 2014; Busse, Roth et al., 2017; Mukherjee, Sathanoori et al., 2017; Choi, Dewar et al., 2018; Peterson, Van Dyke et al., 2018; Rack, van den Berg et al. 2019).

In this review, we highlight gaps in the traditional techniques and how genome-wide changes can be more effectively and efficiently detected using array-based approaches. Key genome wide changes such as microdeletions, amplifications, loss of heterozygosity and ploidy changes will be explored. The literature specific to multiple myeloma (MM), acute lymphoblastic leukaemia (ALL), myeloid disorders and chronic lymphoblastic leukaemia (CLL) will be discussed to illustrate the impact of these new technologies for detection of genome wide aberrations.

2. Traditional cytogenetic approaches

Analysis of metaphases for the investigation of haematological diseases has been the standard methodology for assessing the whole genome since the discovery of the Philadelphia (Ph') chromosome in 1960 by Nowell and Hungerford (Whang, Frei et al., 1963, Krauss, Sokal et al., 1964; Nowell, 2007). Whilst both technology and our understanding of the cancer genome have improved significantly, the use of karyotyping of metaphase spreads is still considered the 'gold standard' for many hematological investigations (Fig. 1). The current investigative guidelines such as those by the National Comprehensive Cancer Network (NCCN) (Brown, Shah et al., 2017), the European LeukaemiaNet (ELN) (Dohner, Estey et al., 2017) and the American College of Medical Genetics and Genomics (ACMG) (Mikhail, Heerema et al., 2016) include karyotyping in their set of diagnostic tools required for haematological malignancy investigations.

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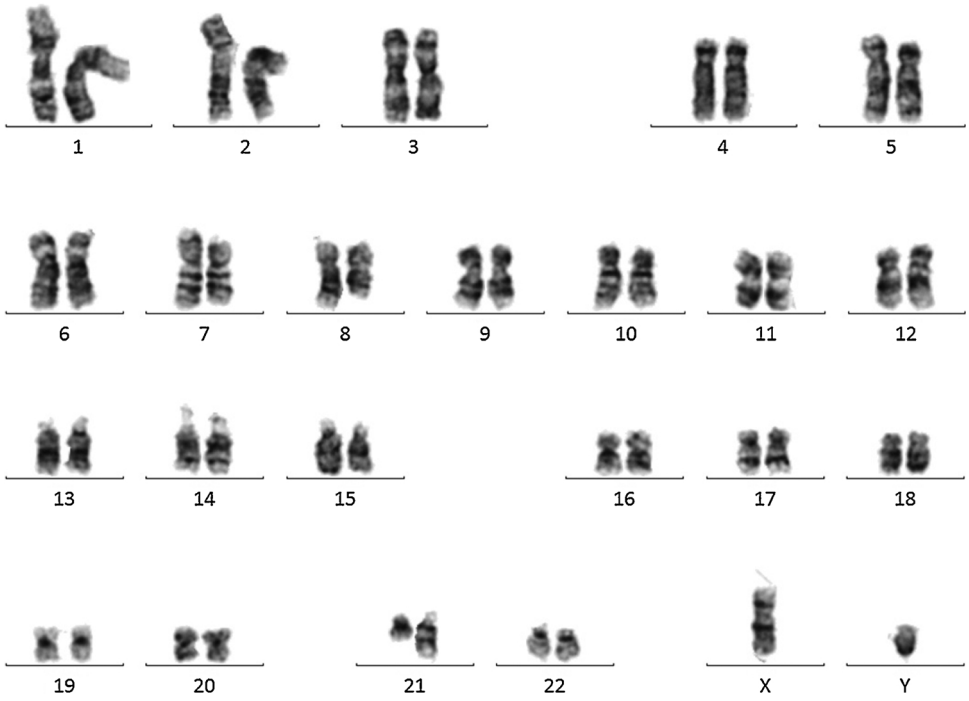

Fig. 1. A G-banded karyotype, showing a t(8;21)(q22;q22), is a standard cytogenetic tool for investigation of haematological malignancies.

The use of karyotyping has been used for the genomic classification of haematological malignancies described by the World Health Organisation (WHO) (Swerdlow SH 2017). Studies have shown these categories to be associated with a particular disease course, risk of relapse, overall survival and event free survival (Heim, 2015; Swerdlow et al., 2017).

The ability to detect copy number variations (CNV's), balanced and unbalanced translocations or rearrangements and evidence of multiple clonal populations has been the strength of using karyotype. However, there are considerable limitations to this methodology, such as its very low resolution of 5-10Mb or less on metaphase preparations. This has resulted in the misinterpretation of structural findings and the reporting of an apparently 'normal' results, since many of the aberrations are below the resolution of this type of assay (Bajaj, Xu et al., 2011; Arsham and Lawce, 2017).

The ability to obtain metaphases representative of the disease being investigated can also be extremely difficult for some malignancies, such as late B-cell and T-cell malignancies, which require the addition of mitogens and interleukins to stimulate the division of abnormal cells. This can lead to the detection and analysis of only normal cell populations and not target malignant clones (Cooley, Lebo et al., 2013; Heim, 2015; Arsham and Lawce, 2017). Studies show that abnormal karyotypes are seen in varying proportions such as in only 20–40% of patients with multiple myeloma (MM) (Sawyer, 2011); (Nahi, Sutlu et al., 2011); (Zhan, Sawyer et al., 2006; Dimopoulos, Kyle et al. 2011), 60% of patients with acute lymphoblastic leukaemia (ALL) (Nordgren, Heyman et al., 2002), 40% of chronic lymphoblastic leukaemia (CLL) patients (Juliusson, Oscier et al. 1990) and 40–50% of acute myeloid leukaemia (AML) patients (Grimwade, Walker et al., 1998; Byrd, Mrózek et al., 2002; Mrózek, Heerema et al., 2004; Schlenk, Döhner et al. 2008). Whilst not all abnormal clones in haematological disease have cytogenetically detectable changes, this data suggests there are significant limitations to this technique.

The introduction of the fluorescent *in situ* hybridisation (FISH) in the 1980's overcame the need for dividing cells with the ability to investigate chromosomal changes at the gene level using fluorescent markers that could be microscopically observed (Arsham and Lawce, 2017); (Levsky and Singer, 2003). Subsequently, during the 1990's a popular, laborious but expensive method of multiplex and whole chromosome paint FISH techniques was used to assess whole chromosomes or the whole genome for changes. Whilst innovative at the time, it's brief use was quickly overtaken by early array-based technologies (Speicher, Ballard et al., 1996; Trask, 2002). Today, FISH probes are predominantly used to target specific DNA sequences of ˜100-600 kb in size and are not used to assess the whole genome, but are often used to target areas of known prognostic significance i.e. common reoccurring regions of copy number change and translocations or rearrangements involving specific genes (Levsky and Singer, 2003; Arsham and Lawce, 2017).

FISH is now widely used to complement karyotyping in haematological cytogenetic investigations and is often the preferred method of detection for clinically relevant or actionable changes where karyotyping is limiting or negative or where a specific urgent result is required (Hallek, Cheson et al., 2008, Medeiros, Othus et al., 2014; Palumbo, Avet-Loiseau et al., 2015, Dohner, Estey et al..2017). Many research groups including the International Myeloma Working Group (IMWG) and the International Workshop on Chronic Lymphocytic Leukemia (IWCLL) recommend the use of FISH as the priority test for the diagnostic workup for patients with MM and CLL (Hallek, Cheson et al., 2008, Palumbo, Avet-Loiseau et al., 2015).

A much larger percentage of high-risk patients are identified using FISH. Up to 95% of cases have changes identified by FISH studies in MM (Munshi et al., 2011a, 2011b; Palumbo, Avet-Loiseau et al., 2015), ˜ 80% in CLL (Hallek, Cheson et al., 2008) and ˜89% of cases in ALL (Harrison, Moorman et al., 2005), thereby indicating the superiority of FISH over standard karyotyping.

While the combination of karyotype and FISH analysis is the current standard of practice for clinical genomic investigations for the detection of CNV's and gene rearrangements in haematological malignancies, more recent studies have shown that certain genome wide changes may still be missed (Simons, Sikkema-Raddatz et al., 2012, Malhotra, Lindberg et al., 2013; Rode, Maass et al., 2016, Mukherjee, Sathanoori et al., 2017). The need for higher resolution across the whole genome, a more robust, accurate and definitive investigation of changes within the genome, detection of copy neutral loss of heterozygosity (cnLOH) and the investigation of a considerably larger range of known and novel

fusion genes is critical for a personalised approach to treatment strategies in haematological malignancies.

3. Clinical utility of SNP-microarray

The diagnosis, classification, prognostication, risk stratification, disease monitoring and therapy selection for haematological disease are rapidly evolving. This evolution can be largely attributed to the advances in technology that allow the detection of known and novel changes associated with disease at much higher resolution with greater specificity and sensitivity as well as the development of targeted therapies (Braggio, Egan et al., 2013, Black, Salto-Tellez et al., 2015; Surrey, Luo et al., 2016, Hay, Hatton et al., 2017).

Chromosomal microarray (CMA) is a technique that has several variations such as those with only oligonucleotide probes, oligonucleotide + single nucleotide polymorphism (SNP) probes or SNP only content. However, in clinical practice, CMA's that include SNP content due to their ability to provide genotype information are more widely used. This allows for the detection of copy-neutral loss of heterozygosity (cn-LOH), provides confirmation of CNV's and also clarifies polyploid imbalances (Mikhail, Heerema et al., 2016, Schoumans, Suela et al., 2016; Peterson, Van Dyke et al., 2018).

The past decade has seen a large body of compelling evidence reported that highlights the effectiveness and clinical utility of SNP-microarrays for the investigation of haematological malignancies (Shao, Kang et al., 2010, Slovak, Smith et al., 2010; Yasar, Karadogan et al. 2010; Sawyer, 2011; Tiu, Gondek et al., 2011, Veigaard, Norgaard et al., 2011; Simons, Sikkema-Raddatz et al., 2012, Schoumans, Suela et al., 2016; Surrey, Luo et al., 2016, Mukherjee, Sathanoori et al., 2017). There has also been reference to the use of microarray technology to investigate genomic changes where karyotyping and FISH are limiting as well as the inclusion of malignant microarray nomenclature in the international system of human cytogenetic nomenclature (ISCN) (McGowan-Jordan, Simons et al., 2016, Mikhail, Heerema et al., 2016; Stevens-Kroef, Simons et al., 2017). The specific situations where traditional techniques are not sensitive and CMAs can provide better clinically relevant information are discussed in greater detail in the following sections.

3.1. Microdeletion and amplification detection

Genome wide association studies (GWAS) of many haematological malignancies such as paediatric acute lymphoblastic leukaemia (ALL), multiple myeloma (MM), chronic lymphoblastic leukaemia (CLL) and acute myeloid leukaemia (AML) have identified genomic aberrations that are associated with an increased risk of relapse, drug responsiveness and early minimal residual disease (MRD) response (Yang, Cheng et al. 2009, 2011; Evans, Milne et al. 2014; Coleman, Lee et al. 2015; Berndt, Camp et al. 2016; Mitchell, Li et al. 2016; Papaemmanuil, Gerstung et al. 2016; Vijayakrishnan, Studd et al. 2018). It is evident that conventional karyotyping, FISH and sequencing are able to detect many known risk-associated genomic alterations; however, there are many new and prognostically important aberrations that are not easily identified by these methods, including microdeletions and amplifications (Pui and Evans, 2013; Stanulla, Dagdan et al. 2018).

There is a large amount of evidence from recent studies showing small focal intragenic deletions are associated with haematological disease (Tsao, Draoua et al. 2004; Meijerink, den Boer et al. 2009; Harrison, Haas et al. 2010; Mullighan, 2012; Pui, Mullighan et al. 2012; Van Vlierberghe and Ferrando, 2012; Zhang, Ding et al. 2012; Baughn, Biegel et al. 2015; Ghazavi, Lammens et al. 2015; Hunger and Mullighan, 2015; Roberts and Mullighan, 2015; He, Abdel-Wahab et al. 2016; Olsson, Zettermark et al. 2016; Stanulla, Dagdan et al. 2018; Sutton, Venn et al. 2018). These microdeletions may explain why some patients with standard risk (SR) and intermediate risk (IR) continue to relapse and have poor outcomes regardless of the impressive predictive values of MRD, clinical and laboratory risk factors (Borowitz, Devidas et al. 2008; Baughn, Biegel et al. 2015).

The gene, *IKZF1*, has been identified as an important transcription factor and tumour suppressor associated with the pathogenesis of ALL. Its' association with extremely poor event-free survival (EFS) is also being evaluated in other haematological diseases such as MM (Krönke, Kuchenbauer et al. 2016) and myeloid malignancies (Jäger, Gisslinger et al. 2010; de Rooij et al., 2015; Soverini, de Benedittis et al. 2015). Microdeletions and cnLOH often affect *IKZF1* and its detection by SNP-microarray is important for assessing the genomic risk in lymphoid malignancies and risk of transformation in myeloid malignancies (Jäger, Gisslinger et al. 2010; Grossmann, Kohlmann et al. 2011).

A new prognostically independent genomic group, termed IKZF1^{PLUS}, has provided evidence of the importance of microdeletion detection at diagnosis in B-ALL. This entity is defined as having a deletion (intragenic or whole gene deletion) of *IKZF1* in conjunction with one or more deletions of *PAX5*, *CDKN2A*, *CDKN2B* or the PAR1 region and in the absence of an *ERG* deletion; this sub-group of B-ALL patients are extremely susceptible to relapse and their detection has influenced the change of treatment protocols from the Associazione Italiana di Ematologia ed Oncologia Pediatrica and the Berlin-*Frankfurt-Muenster* (AIEOP-BFM) ALL trials (Stanulla, Dagdan et al. 2018).

Focal gene amplification is a common feature of solid tumours; however, it is also observed in haematological malignancies. The mechanisim of amplification leads to over-expression of oncogenes, which most commonly increases cell proliferation (Albertson, 2006; Dang, 2015; Ohshima, Hatakeyama et al. 2017). One of the most frequently observed amplifications in haematological malignancies is the iAMP21. This is associated with high-risk B-cell ALL and is often detected with the use of FISH for the *RUNX1* gene (Harrison, 2015). However, more recent studies reveal the genomic complexity associated with the amplification is far greater that that observed by FISH techniques alone (Heerema, Carroll et al. 2013; Harrison et al., 2014; Baughn, Biegel et al. 2015; Harrison, 2015).

Amplifications are also observed in myeloid malignancies, such as the whole gene amplification of *KMT2A* and *MYC*, are commonly associated with therapy related or transforming MDS and AML (Papenhausen, Griffin et al. 2005; Angelova, Jordanova et al. 2011; Tang, DiNardo et al. 2015; L'Abbate, Tolomeo et al. 2018). A partial tandam duplication of *KMT2A* (PTD-KMT2A), which is often not detectable by FISH or karyotype due to its size and location, is also detectable by SNP-microarray (Whitman, Liu et al. 2005; Swerdlow et al., 2017; Choi, Dewar et al. 2018). The prognostic significance associated with these amplifications highlights the importance of their detection.

Fusion forming microdeletions and amplifications, which are detectable by SNP-microarray, such as the deletion forming the *STIL-TAL1, CLRF2-P2RY8, EBF1-PDGFRB* and the *FIPIL1-PDGFRA* fusion genes and the amplification forming the *NUP214-ABL1* fusion gene are not detectable by karyotype. While FISH is an effective method used for their detection, this technique is not widely available in diagnostic laboratories as some of these changes are rare. The detection of such microdeletions and amplifications by SNP-microarray can provide prognostic information about risk of relapse and the potential for targeted therapy selection (D'Angio et al., 2015; Schwab, Ryan et al. 2016; Busse, Roth et al. 2017; Roberts, Reshmi et al. 2018).

A new entity of ALL, known as BCR-ABL1-like, is often associated with the formation of fusion genes leading to tyrosine kinase activation or other fusions resulting in the truncation and activation of the erythropoietin receptor (*EPOR*) and *JAK* mutations (Boer, Steeghs et al. 2017; Reshmi, Harvey et al. 2017; Roberts, Reshmi et al. 2018). Many of these changes (*CLRF2-P2RY8, EBF1-PDGFRB, NUP214-ABL1)* are often associated with small microdeletions and duplications, which are detectable by SNP-microarray. Some patients in this subgroup, particularly those with an *EBF1-PDGFRB* fusion, show exceptional response to tyrosine kinase inhibitor (TKI) therapy – a powerful example showing the importance of identifying small CNV's known to directly

impact therapy and patient outcome (Arber, Orazi et al. 2016; Schwab, Ryan et al. 2016).

SNP-microarray analysis has proven to be a useful tool in predicting the fusion genes in both lymphoid and myeloid haematological malignancies as well as in some solid tumours (Kawamata, Ogawa et al. 2008; Dougherty, Wilmoth et al. 2011; Busse, Roth et al. 2017). Busse et al. identified interstitial deletions were the cause of fusion genes in approximately 25% of haematological and over two-thirds of their solid tumour patients. In their study, small CNV's were identified at the fusion gene loci in one-third of haematological and one-fifth of solid tumour cases (Busse, Roth et al. 2017). It Is recognised, however, that not all fusion genes are associated with deletions or duplications and can be balanced. Hence, SNP-microarray analysis can be a useful tool to help identify those fusions which are unbalanced and be used to complement other tools specifically designed to identify fusion genes, such as sequencing fusion panels and FISH studies (Kawamata, Ogawa et al. 2008; Dougherty, Wilmoth et al. 2011; Busse, Roth et al. 2017; Rack, van den Berg et al. 2019).

3.2. Copy neutral loss of heterozygosity (cnLOH) detection and masked ploidy

SNP-microarray data has a significant advantage over karyotyping and FISH methods as it can reliably detect regions of cnLOH across the whole genome – even in clonally heterogeneous samples. There is a high prevalence of cnLOH in haematological malignancies, not appreciated until the introduction of SNP-microarray studies (Young, Debernardi et al. 2006).

Regions of cnLOH can often harbor mutations leading to the mutational inactivation of tumour suppressor genes such as *TP53* and *TET2* or oncogenic driver mutations that include *JAK2, C-KIT* and *FLT3*. Here, the deletion of a non-mutated allele occurs and reduplication of the mutated allele transpires as a 'rescue' event, which results in the presence of two mutated alleles (Paskulin, Giacomazzi et al. 2014; Jeffries, Trim et al. 2015; Duployez, Boudry-Labis et al. 2018).

It has been shown that up to 20% of normal AML karyotypes harbor somatic cnLOH (Young, Debernardi et al. 2006). Recent studies show cnLOH of chromosome 7/7q has a similar prognosis to the well established poor prognostic marker del(7q)/-7 in MDS (Jerez, Sugimoto et al. 2012; Gondek and DeZern, 2014; da Silva et al., 2017; Makishima, Yoshizato et al. 2018; Ogawa, 2019). In other diseases such as Waldenström macroglobulinemia, which is usually karyotypically normal, has uncovered potential target genes within regions of cnLOH (Poulain, Roumier et al. 2013). There is increasing evidence that regions of cnLOH can affect the prognostication and management of patients with haematological disease (Gorringe, 2001; Nowak, Ogawa et al. 2010; Sawyer, 2011; Tiu, Gondek et al. 2011; Simons, Sikkema-Raddatz et al. 2012; Moorman, Enshaei et al. 2014; Paskulin, Giacomazzi et al. 2014; Renneville, Abdelali et al. 2014; Baughn, Biegel et al. 2015; Hunger and Mullighan, 2015; Duployez, Boudry-Labis et al. 2018).

Hypodiploidy and near-haploidy are categories of B-cell ALL associated with a high genomic risk and poor outcomes. Detection of these genomes is difficult when using traditional cytogentic methods, hence, SNP-microarray has been identified as the most appropriate method to uncover masked hypodiploidy and near-haploidy (Fig. 2) (Baughn, Biegel et al. 2015; Hunger and Mullighan, 2015; Safavi, Olsson et al. 2015; Schoumans, Suela et al. 2016; Wang, Miller et al. 2016; Peterson, Van Dyke et al. 2018).

3.3. Complex genomic signature detection

There are two recently described complex genomic aberrations, chromothripsis (Fig. 3) and chromoanasynthesis (Fig. 4). Both of these changes indicate complex events associated with end-stage or relapsed disease and poor clinical outcomes in haematological malignancies (Magrangeas, Avet-Loiseau et al. 2011; Forment, Kaidi et al. 2012; Jones and Jallepalli, 2012; Righolt and Mai, 2012). These changes have only become apparent with the increasing use of SNP-microarray and paired end sequencing techniques. Chromothripsis and chromoanasynthesis are different in nature to complex step-wise events (Fig. 5), which is the accumulation of aberrations over time, as the aberrations occur as a sudden stochastic event in a cancer cell leading to specific patterns of genomic aberrations (Stephens, Greenman et al. 2011; Berry, Dixon-McIver et al. 2017).

Chromothripsis is a phenomenon characterised by a pattern of copy number loss localised to a chromosome arm or segment showing oscillation between copy number changes, which are acquired at one time point rather than over many cell cycles (Fig. 3).

On the other hand, chromoanasynthesis is characterised by an oscillating pattern of copy number gain. It is also localised to a chromosome arm or region and is acquired at one time point (Holland and Cleveland, 2012; Righolt and Mai, 2012; Zhang, Leibowitz et al. 2013; Liu, Stevens et al., 2014). Both chromothripsis and chromoanasynthesis exhibit uniquely identifiable genomic signatures on SNP-microarray that enable their detection in one simple assay (Fig. 4).

The instability of a cell can inititate a cascade of events leading to the progressive accumulation of genomic changes over time. This is particularly evident in the progression of disease from one that has a relatively stable existence, such as monoclonal gammopathy of unknown significance (MGUS), to a highly proliferative disorder as seen in MM and plasma cell leukaemia (PCL) (Sawyer, 2011; Rossi, Voigtlaender et al. 2017).

All of these complex genomic events are not only identifiable using SNP-microarray, but were also defined by this modality, the characterisation of which was not possible by karyotyping and FISH analysis alone (Magrangeas, Avet-Loiseau et al. 2011; Sawyer, 2011; Kim, Xi et al. 2013; Malhotra, Lindberg et al. 2013; Cai, Kumar et al. 2014; Kloosterman, Koster et al. 2014; McEvoy, Nagahawatte et al. 2014; Abáigar, Robledo et al. 2016; Bochtler, Granzow et al. 2017).

3.4. Accurate interpretation of genomic changes otherwise not defined

The genomic information provided by karyotyping is low-resolution in comparison to SNP-microarray and many changes can easily be misinterpreted or left completely undefined. The pattern recognition of chromosome banding by a trained scientist contrasts with quantitative data analysis provided by SNP-microarray. The ISCN has made provisions for the reporting of findings where there is uncertainty of the identification of chromosomes or chromosome segments (McGowan-Jordan, Simons et al. 2016). For example, an additional chromosome of unidentifiable genomic origin is assigned as a 'marker' chromosome. In this instance, the additional material is a gain of specific genomic material of unknown origin and/or significance. However, using SNP-microarray, the genomic constitution of such additional 'marker' chromosomal material would be identifiable and may provide significant clinically relevant detail not otherwise determined by karyotyping. Indeed, SNP-microarray studies in AML have shown that marker chromosomes as well as ring and derivative chromosomes are often the result of a chromothriptic event and are associated with high-risk disease (Bochtler, Granzow et al. 2017; Fontana, Marconi et al. 2017).

4. Bridging the gap in genomic diagnostic technologies

Accurate identification and definition of genomic aberrations can influence disease classification, patient risk stratification and clinical management options in haematological malignancies (Medeiros, Othus et al. 2014; Duployez, Grzych et al. 2016; Schwab, Ryan et al. 2016; Basha, Smith et al. 2017; Boer, Steeghs et al. 2017; Busse, Roth et al. 2017; Duployez, Boudry-Labis et al. 2018; Stanulla, Dagdan et al. 2018).

There have been significant developments in the detection of

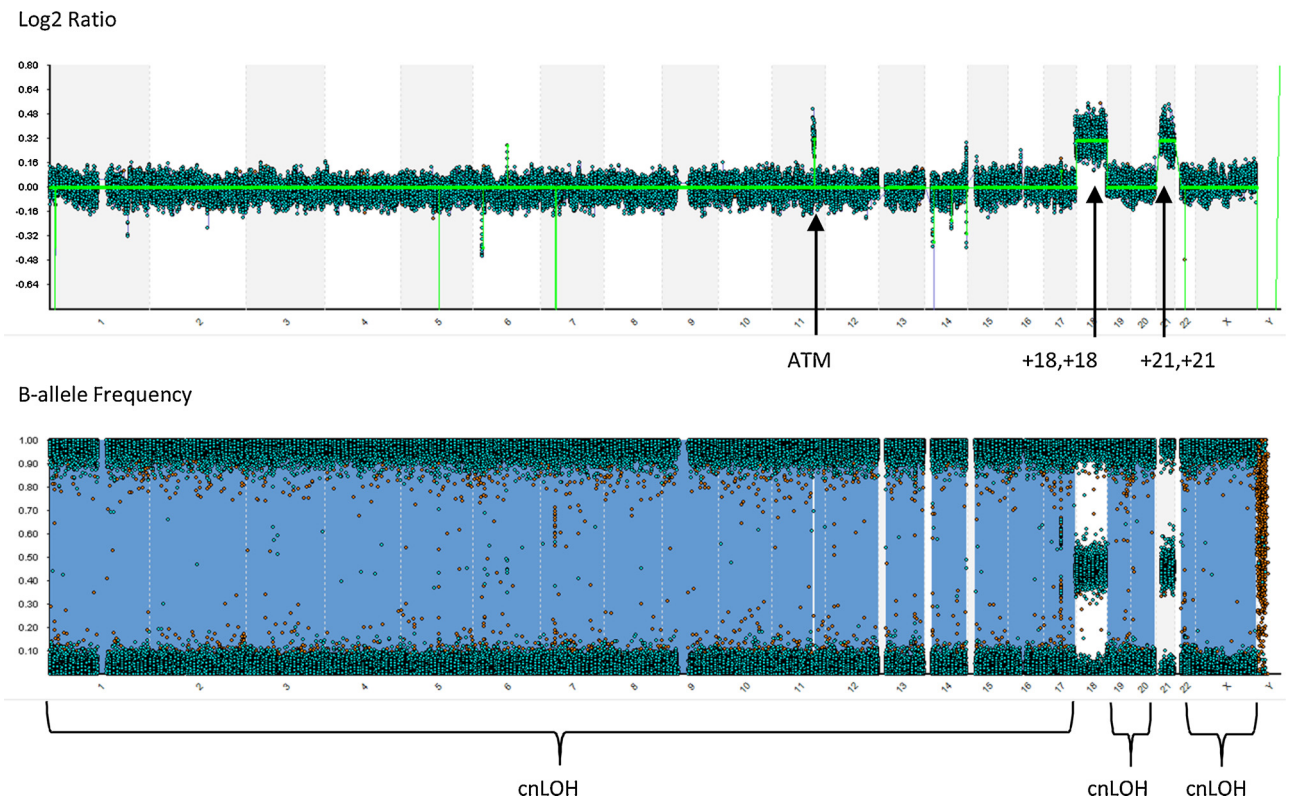

Fig. 2. Whole genome view from a SNP-microarray performed on the diagnostic bone marrow specimen submitted for investigation of ALL. Top plot shows the log2 ratio achieved across the genome and indicates two additional copies of 11q22.3 and whole chromosomes 18 and 21. The B-allele frequency plot (lower plot) indicates copy-neutral loss of heterozygosity for chromosomes 1–19, 22 and X.

mutations associated with the diagnosis, risk stratification, prognostication and treatment management of haematological malignancies (Black, Salto-Tellez et al. 2015). The introduction of massively parallel sequencing (MPS) has uncovered clinically actionable mutations and redefined the categorisation and risk stratification of disease, particularly in myeloid disorders (Dohner, Estey et al. 2017; Greenberg, Stone et al. 2017). While MPS can uncover regions of copy number changes and allude to the existence of fusion genes, it is currently not an efficient or effective way to detect such changes across the whole genome. A whole genome or whole exome approach would be required rather than the targeted approach used in current clinical pratice (Bolli, Bignell et al. 2014; Black, Salto-Tellez et al. 2015; Shen, Szankasi et al. 2015).

The limitations of MPS, FISH and karyotype highlight a large gap in the use of technology to detect clinically relevant changes known to be associated with haematological disease. The translation of high definition single nucleotide polymorphism (SNP) microarray into clinical use for the detection of CNV's and regions of LOH in haematological malignancy is an effective solution to bridge the gap in technological applications between karyotype, FISH panels and MPS (Mikhail, Heerema et al. 2016; Schoumans, Suela et al. 2016; Peterson, Van Dyke et al. 2018).

5. Can SNP-microarray be a tier 1 clinical investigation for detecting genome wide gains and losses in haematological malignancies?

5.1. Technical aspects

This section discusses the technical challenges including sensitivity, ability to detect complex clonal changes and limitations of SNP microarrays. This is followed by a discussion of current consensus on its use as well as a brief economic perspective.

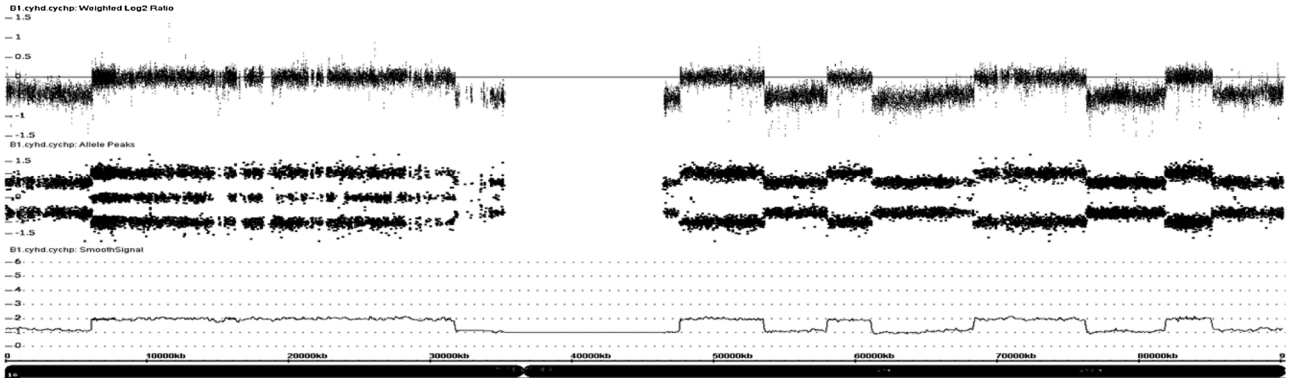

Fig. 3. Chromothripsis identified by SNP-microarray on chromosome 16 in multiple myeloma (Berry, Dixon-McIver et al. 2017).

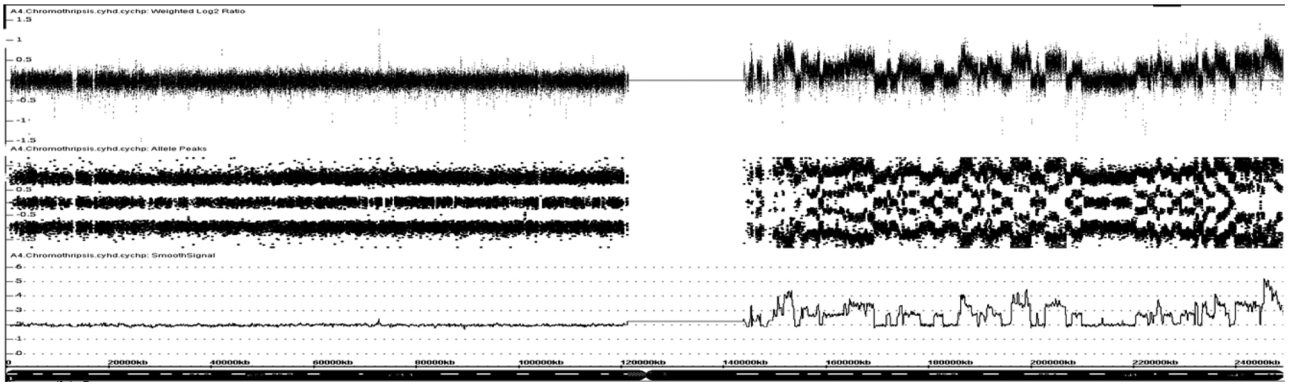

Fig. 4. Chromoanasynthesis identified by SNP-microarray on chromosome 1q in multiple myeloma (Berry, Dixon-McIver et al. 2017).

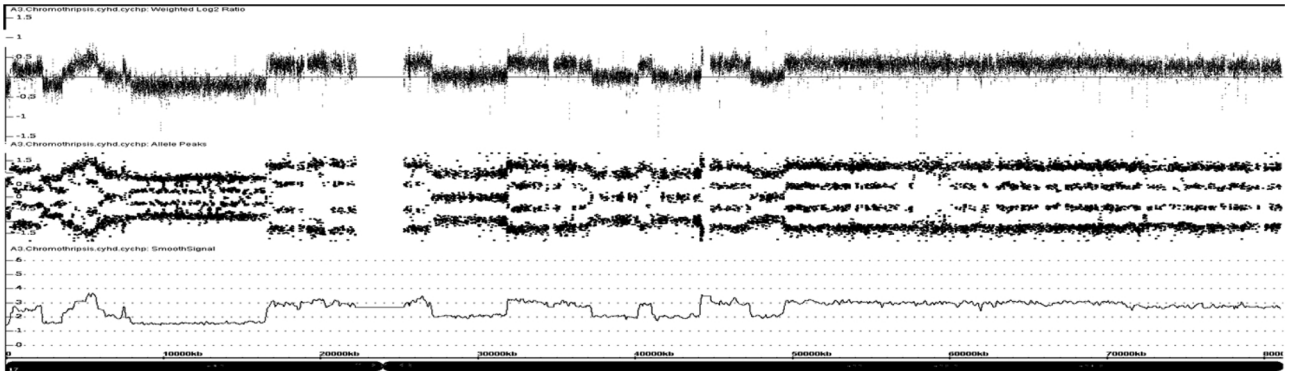

Fig. 5. A combination of a complex step-wise event and chromoanasynthesis identified by SNP-microarray (Berry, Dixon-McIver et al. 2017).

5.1.1. Sensitivity

The standard traditional cytogenetic investigation of karyotype requires the analysis of 20 metaphase cells (Mikhail, Heerema et al. 2016) with a sensitivity of about 10% (Maciejewski, Tiu et al. 2009; Mikhail, Heerema et al. 2016). The practical reporting sensitivity of FISH also include a measurement of uncertainty, which represents around 3–10% tumour burden (Stevens-Kroef, Weghuis et al. 2012; Arsham and Lawce, 2017; Wan, 2017). Sometimes, a higher sensitivity can be achieved with specific break-apart or dual fusion probes (Dewald, Wyatt et al. 1998; Wolff, Bagg et al. 2007; Mallo, Arenillas et al. 2008; Göhring, Giagounidis et al. 2011; Wan, 2017).

A high-density SNP-array can detect changes in a sample with 10–20% tumour burden (Schoumans, Suela et al. 2016; Peterson, Van Dyke et al. 2018). This approach detects CNV's and cnLOH in an unbiased manner; however, cannot detect changes in lower level clones (< 10%) (Table 1). This limitation can be reduced in some circumstances with the enrichment of the cell population to be examined, such as in MM where the CD138+ plasma cells are isolated before DNA extraction (Stevens-Kroef, Weghuis et al. 2012; Berry, Bain et al. 2013; Boneva, Brazma et al. 2014).

5.1.2. Clonal complexity

An estimate of clonal involvement can be made utilizing both the log2 ratio and the B-allele frequency plots provided by the SNP-array data for each aberration observed (Cheng, Dai et al. 2017; Martinez, Kimberley et al. 2017). The differences observed in the log2 ratio and B-allele between each genomic imbalance may indicate the presence of multiple clones but cannot definitively detail which aberrations are in which clone. However, clonal heterogeneity may be difficult to estimate accurately if there are several minor clones.

The use of genome wide MPS for DNA sequencing enables the assessment of single nucleotide variants (SNV's), small insertions or deletions (indels), copy number variation (CNV) and structural variants (SV's) such as gene fusions. A number of mutations such as in those in *FLT3, C-KIT, CEBPA, IDH1/2, RUNX1, JAK2* and *TP53 are clinically relevant in haematological malignancies*. These changes are generally < 1 kb in size and often only involve one or several base-pairs (bp), which is well below the resolution and capability of a SNP-microarray (Kadia, Jain et al. 2016; Dohner, Estey et al. 2017; Jennings, Arcila et al. 2017). However, some deletion mutations, such as those involving *PTEN, CDKN2A, IKZF1* and *TP53* are large enough (> 10 kb) to be detected by high-definition SNP-microarrays making the SNP-microarray a complementary technique (Jenkinson, Kirkwood et al. 2016; Jennings,

Table 1
Attributes of cytogenomic technologies in current clinical practice for haematological malignancy investigations.

	Resolution	Whole genome analysis	cnLOH detection	Dividing cells required	Sensitivity	Balanced rearrangement detection
Karyotype	Very Low	Yes	No	Yes	10%	Yes
FISH	~100-300kb	No	No	No	~5-10%	Yes
SNP-microarray	~3-10 kb	Yes	Yes	No	~5-20%	No
Fusion gene sequencing panels	< 1kb	No	No	No	< 5-10%	Yes
NGS / MPS	< 1kb	Yes	No	No	~5-10%	Yes[a]

[a] = Specifically designed NGS panels or MPS techniques.

Arcila et al. 2017; Stanulla, Dagdan et al. 2018). The use of a targeted panel MPS panel rather than, a genome wide approach, is the favoured method at present due to the cost and more specifically the ease of data interpretation (Aziz, Zhao et al. 2015; Kanagal-Shamanna, Singh et al. 2016; Jennings, Arcila et al. 2017). Therefore, SNP-microarray analysis will continue to be a cost effective option for clinical diagnostics until the cost and ease of genome wide MPS platforms and bioinformatics pipelines makes it scalable for routine diagnostics.

5.2. Current consensus and guidelines on use of microarrays

The widespread use of microarray in the prenatal setting to detect constitutional variants provides a workflow segway for its use in cancer diagnostics (Shaffer, 2005; South, Lee et al. 2013). The use of SNP-microarrays as a complimentary (and possibly superior) technique to standard cytogenetic investigations is increasing (Cooley, Lebo et al. 2013; Rack, van den Berg et al. 2019). This is particularly evident with the recent collaboration of the ACMG and the Cancer Genomics Consortium (CGC) in America working toward the recognition that the adaptation of SNP microarrays to supplant traditional methods in the field of clinical cancer genomics (Akkari, Baughn et al. 2017; Hodge, Kanagal-Shamanna et al. 2017; Miron, Wenger et al. 2017; Raca, Biegel et al. 2017; Akkari, Baugn et al. 2018) as well as the inclusion of microarray testing in the European Society for Medical Oncology (ESMO) guidelines for ALL (Hoelzer, Bassan et al. 2016) and the new recommendations for assessment of haematological neoplasms by the European cytogenomic community (Rack, van den Berg et al. 2019).

5.3. Cost and automation

Conventional karyotype and large panel FISH studies are labour intensive requiring significant manual preparation and comprehensive analysis times (Maciejewski, Tiu et al. 2009; Peterson, Van Dyke et al. 2018). Since the implementation of microarray studies for the investigation of constitutional disorders, the cost of performing a SNP-microarray has decreased considerably. The availability of approved commercial platforms, consumer usage and the technical refinement of the assay have all no doubt contributed to driving down the production cost of the arrays and their required reagents (Gershon, 2002; Trakadis, 2011).

6. Conclusion

The SNP-microarray technology has the potential to replace and improve current clinical and laboratory techniques for risk stratification and therapeutic choice for patients at diagnosis. High density SNP-microarray technology gives a detailed picture of CNV's and cnLOH across the whole genome without the ability of detecting truly balanced translocations or fusion genes. As rearrangements and fusion genes are of significant prognostic importance in some haematological malignancies, it is necessary to complement SNP-microarray analysis with the use of translocation FISH or fusion gene-sequencing panels. The tumour load (> 10–20%) is also a key aspect that will impact the detection of genomic changes; this is important as the sensitivity of SNP-microarrays is limiting for the study of MRD or disease (Rack, van den Berg et al. 2019). Other technologies are rapidly advancing that could be used for MRD such as circulating tumour DNA (ctDNA) analysis (Wan, Massie et al. 2017; Cabel, Proudhon et al. 2018), but this is not the subject of this review.

The incorporation of SNP-microarrays into published guidelines and technical standards by the ACMG (Cooley, Lebo et al. 2013), Schoumans et al, and a recent review by American Society for Clinical Pathology (Peterson, Van Dyke et al. 2018) plus the most recent European recommendations (Rack, van den Berg et al. 2019) emphasize the integration of SNP-microarray analysis into clinical use. The SNP-microarray is a key cost-effective advance that can be incorporated into routine any clinical diagnostic workflow to substantially increase efficiency and improve the detection of important genome wide prognostic and predictive aberrations in haematological malignancies.

Credit author statement

NKB took the lead on the manuscript with the support of RJS and AKE. PR and RJS were responsible for the final review of the manuscript. All authors provided critical feedback and helped shape the manuscript.

Declaration of Competing Interest

We declare that we have no conflicts of interest in the authorship of this contribution.

References

Abáigar, M., Robledo, C., Benito, R., Ramos, F., Díez-Campelo, M., Hermosín, L., et al., 2016. Chromothripsis Is a recurrent genomic abnormality in High-risk myelodysplastic syndromes. PLOS ONE 11 (10), e0164370.

Akkari, Y., Baughn, L., Hagelstrom, R.T., Hiemenz, M., Mikhail, F.M., Shao, L., et al., 2017. Practice guidelines for Genetic/Genomic testing in pediatric B-lineage acute lymphoblastic leukemia (B-ALL): a cancer genomics consortium (CGC) workgroup. Cancer Genetics 214, 38.

Akkari, Y., Baugn, L., Bruyere, H., Hagelstrom, T., Pitel, B., Raca, G., et al., 2018. 19. Evidence-based review of genomic aberrations in T-ALL: strategy and progress of CGC T-ALL working group. Cancer Genetics 226, 43.

Albertson, D.G., 2006. Gene amplification in cancer. Trends in Genetics 22 (8), 447–455.

Angelova, S., Jordanova, M., Spassov, B., Shivarov, V., Simeonova, M., Christov, I., et al., 2011. Amplification of c-MYC and MLL genes as a marker of clonal cell progression in patients with myeloid malignancy and trisomy of chromosomes 8 or 11. Balkan J. Medical Genetics : BJMG 14 (2), 17–24.

Arber, D.A., Orazi, A., Hasserjian, R., Thiele, J., Borowitz, M.J., Le Beau, M.M., et al., 2016. The 2016 revision to the World Health Organization (WHO) classification of myeloid neoplasms and acute leukemia. Blood.

Arsham, M.S.B.M., Lawce, H.J., 2017. The AGT Cytogenetics Laboratory Manual. John Wiley & Sons, Inc, Hoboken, New Jersey.

Aziz, N., Zhao, Q., Bry, L., Driscoll, D.K., Funke, B., Gibson, J.S., et al., 2015. College of American pathologists' laboratory standards for next-generation sequencing clinical tests. Arch. Pathol. Lab. Med. 139 (4), 481–493.

Bajaj, R., Xu, F., Xiang, B., Wilcox, K., Diadamo, A.J., Kumar, R., et al., 2011. Evidence-based genomic diagnosis characterized chromosomal and cryptic imbalances in 30 elderly patients with myelodysplastic syndrome and acute myeloid leukemia. Mol Cytogenet 4, 3.

Basha, B., Smith, J., Rogers, H.J., Cook, J.R., 2017. What Is the clinical utility of repeat SNP array testing in the follow-up of myeloid neoplasms?: A retrospective analysis of 44 patients with serial SNP arrays. Am. J. Clin. Pathol. 147 (3), 278–284.

Baughn, L.B., Biegel, J.A., South, S.T., Smolarek, T.A., Volkert, S., Carroll, A.J., et al., 2015. Integration of cytogenomic data for furthering the characterization of pediatric B-cell acute lymphoblastic leukemia: a multi-institution, multi-platform microarray study. Cancer Genet 208 (1-2), 1–18.

Berndt, S.I., Camp, N.J., Skibola, C.F., Vijai, J., Wang, Z., Gu, J., et al., 2016. Meta-analysis of genome-wide association studies discovers multiple loci for chronic lymphocytic leukemia. Nat. Commun. 7, 10933.

Berry, N., Bain, N., Enjeti, A., Rowlings, P., 2013. Genomic profiling of plasma cell disorders in a clinical setting: integration of microarray and FISH, after CD138 selection of bone marrow. J Clin Pathol.

Berry, N., Dixon-McIver, A., Scott, R., Rowlings, P., Enjeti, A., 2017. Detection of complex genomic signatures associated with risk in plasma cell disorders. Cancer Genetics 218–219, 1–9.

Black, J.S., Salto-Tellez, M., Mills, K.I., Catherwood, M.A., 2015. The impact of next generation sequencing technologies on haematological research – a review. Pathogenesis 2 (1), 9–16.

Bochtler, T., Granzow, M., Stölzel, F., Kunz, C., Mohr, B., Kartal-Kaess, M., et al., 2017. Marker chromosomes can arise from chromothripsis and predict adverse prognosis in acute myeloid leukemia. Blood.

Boer, J.M., Steeghs, E.M., Marchante, J.R., Boeree, A., Beaudoin, J.J., Beverloo, H.B., et al., 2017. Tyrosine kinase fusion genes in pediatric BCR-ABL1-like acute lymphoblastic leukemia. Oncotarget 8 (3), 4618–4628.

Bolli, N., Bignell, G.R., Ganly, P., Papaemmanuil, E., Avet-Loiseau, H., Sperling, A., et al., 2014. A next generation sequencing-based approach to detect Gene mutations, copy number changes and IGH translocations in multiple myeloma. Blood 124 (21) 3364-3364.

Boneva, T., Brazma, D., Gancheva, K., Howard-Reeves, J., Raynov, J., Grace, C., et al., 2014. Can genome array screening replace FISH as a front-line test in multiple myeloma? Genes. Chromosomes Cancer.

Borowitz, M.J., Devidas, M., Hunger, S.P., Bowman, W.P., Carroll, A.J., Carroll, W.L., et al., 2008. Clinical Significance of Minimal Residual Disease in Childhood Acute Lymphoblastic Leukemia and Its Relationship to Other Prognostic Factors: a

Children'S Oncology Group Study.
Braggio, E., Egan, J.B., Fonseca, R., Stewart, A.K., 2013. Lessons from next-generation sequencing analysis in hematological malignancies. Blood Cancer Journal 3, e127.
Brown, P.A., Shah, B., Fathi, A., Wieduwilt, M., Advani, A., Aoun, P., et al., 2017. NCCN guidelines insights: acute lymphoblastic leukemia, version 1.2017. J Natl Compr Canc Netw 15 (9), 1091–1102.
Busse, T.M., Roth, J.J., Wilmoth, D., Wainwright, L., Tooke, L., Biegel, J.A., 2017. Copy number alterations determined by single nucleotide polymorphism array testing in the clinical laboratory are indicative of gene fusions in pediatric cancer patients. Genes. Chromosomes Cancer 56 (10), 730–749.
Byrd, J.C., Mrózek, K., Dodge, R.K., Carroll, A.J., Edwards, C.G., Arthur, D.C., et al., 2002. Pretreatment cytogenetic abnormalities are predictive of induction success, cumulative incidence of relapse, and overall survival in adult patients with de novo acute myeloid leukemia: results from cancer and leukemia group B (CALGB 8461). Span Class = "Subtitle" Presented in Part at the 43rd Annual Meeting of the American Society of Hematology and published in abstract form. < sup > 59 < /sup > < / span > 100(13): 4325-4336.
Cabel, L., Proudhon, C., Romano, E., Girard, N., Lantz, O., Stern, M.-H., et al., 2018. Clinical potential of circulating tumour DNA in patients receiving anticancer immunotherapy. Nature Reviews Clinical Oncology 15 (10), 639–650.
Cai, H., Kumar, N., Bagheri, H.C., von Mering, C., Robinson, M.D., Baudis, M., 2014. Chromothripsis-like patterns are recurring but heterogeneously distributed features in a survey of 22,347 cancer genome screens. BMC Genomics 15, 82.
Cheng, Y., Dai, J.Y., Paulson, T.G., Wang, X., Li, X., Reid, B.J., et al., 2017. Quantification of multiple tumor clones using Gene array and sequencing data. The annals of applied statistics 11 (2), 967–991.
Choi, S.M., Dewar, R., Burke, P.W., Shao, L., 2018. Partial tandem duplication of KMT2A (MLL) may predict a subset of myelodysplastic syndrome with unique characteristics and poor outcome. Haematologica 103 (3), e131–e134.
Coleman, E.A., Lee, J.Y., Erickson, S.W., Goodwin, J.A., Sanathkumar, N., Raj, V.R., et al., 2015. GWAS of 972 autologous stem cell recipients with multiple myeloma identifies 11 genetic variants associated with chemotherapy-induced oral mucositis. Supportive Care in Cancer 23 (3), 841–849.
Cooley, L.D., Lebo, M., Li, M.M., Slovak, M.L., Wolff, D.J., G. Working Group of the American College of Medical, et al., 2013. American College of medical genetics and genomics technical standards and guidelines: microarray analysis for chromosome abnormalities in neoplastic disorders. Genet. Med. 15 (6), 484–494.
D'Angio, M., Valsecchi, M.G., Testi, A.M., Conter, V., Nunes, V., Parasole, R., et al., 2015. Clinical features and outcome of SIL/TAL1-positive T-cell acute lymphoblastic leukemia in children and adolescents: a 10-year experience of the AIEOP group. Haematologica 100 (1), e10–13.
da Silva, F.B., Machado-Neto, J.A., Bertini, V.H.L.L., Velloso, E.D.R.P., Ratis, C.A., Calado, R.T., et al., 2017. Single-nucleotide polymorphism array (SNP-a) improves the identification of chromosomal abnormalities by metaphase cytogenetics in myelodysplastic syndrome. J. Clin. Pathol. 70 (5), 435–442.
Dang, Chi V., 2015. Web of the extended myc network captures metabolism for tumorigenesis. Cancer Cell 27 (2), 160–162.
de Rooij, J.D.E., Beuling, E., van den Heuvel-Eibrink, M.M., Obulkasim, A., Baruchel, A., Trka, J., et al., 2015. Recurrent deletions of IKZF1 in pediatric acute myeloid leukemia. Haematologica 100 (9), 1151–1159.
Dewald, G.W., Wyatt, W.A., Juneau, A.L., Carlson, R.O., Zinsmeister, A.R., Jalal, S.M., et al., 1998. Highly Sensitive Fluorescence In Situ Hybridization Method to Detect Double BCR/ABL Fusion and Monitor Response to Therapy in Chronic Myeloid Leukemia. Blood 91 (9), 3357–3365.
Dimopoulos, M., Kyle, R., Fermand, J.P., Rajkumar, S.V., San Miguel, J., Chanan-Khan, A., et al., 2011. Guidelines for standard investigative workup: report of the International myeloma workshop consensus panel 3. Blood.
Dohner, H., Estey, E., Grimwade, D., Amadori, S., Appelbaum, F.R., Buchner, T., et al., 2017. Diagnosis and management of AML in adults: 2017 ELN recommendations from an international expert panel. Blood 129 (4), 424–447.
Dougherty, M.J., Wilmoth, D.M., Tooke, L.S., Shaikh, T.H., Gai, X., Hakonarson, H., et al., 2011. Implementation of high resolution single nucleotide polymorphism array analysis as a clinical test for patients with hematologic malignancies. Cancer Genet 204 (1), 26–38.
Duployez, N., Boudry-Labis, E., Roumier, C., Boissel, N., Petit, A., Geffroy, S., et al., 2018. SNP-array lesions in core binding factor acute myeloid leukemia. Oncotarget 9 (5), 6478–6489.
Duployez, N., Grzych, G., Ducourneau, B., Alarcon Fuentes, M., Grardel, N., Boyer, T., et al., 2016. NUP214-ABL1 fusion defines a rare subtype of B-cell precursor acute lymphoblastic leukemia that could benefit from tyrosine kinase inhibitors. Haematologica 101 (4), e133–134.
Evans, T.J., Milne, E., Anderson, D., de Klerk, N.H., Jamieson, S.E., Talseth-Palmer, B.A., et al., 2014. Confirmation of childhood acute lymphoblastic leukemia variants, ARID5B and IKZF1, and interaction with parental environmental exposures. PLoS One 9 (10), e110255.
Fontana, M.C., Marconi, G., Feenstra, J.D.M., Fonzi, E., Papayannidis, C., di Rorá, A.G.L., et al., 2017. Chromothripsis in Acute Myeloid Leukemia: Biological Features and Impact on Survival. Leukemia.
Forment, J.V., Kaidi, A., Jackson, S.P., 2012. Chromothripsis and cancer: causes and consequences of chromosome shattering. Nat. Rev. Cancer 12 (10), 663–670.
Genetics, A. W. G. o.t. A. C. o. M, C. Genomics Laboratory Quality Assurance, 2013. American College of medical genetics and genomics technical standards and guidelines: microarray analysis for chromosome abnormalities in neoplastic disorders. Genet. Med. 15 (6), 484–494.
Gershon, D., 2002. An array of opportunities. Nature 416, 885.
Ghazavi, F., Lammens, T., Van Roy, N., Poppe, B., Speleman, F., Benoit, Y., et al., 2015. Molecular basis and clinical significance of genetic aberrations in B-cell precursor acute lymphoblastic leukemia. Exp. Hematol. 43 (8), 640–653.
Göhring, G., Giagounidis, A., Büsche, G., Hofmann, W., Kreipe, H.H., Fenaux, P., et al., 2011. Cytogenetic follow-up by karyotyping and fluorescence in situ hybridization: implications for monitoring patients with myelodysplastic syndrome and deletion 5q treated with lenalidomide. Haematologica 96 (2), 319–322.
Gondek, L.P., DeZern, A.E., 2014. I Walk the line: how to Tell MDS from other bone marrow failure conditions. Current Hematologic Malignancy Reports 9 (4), 389–399.
Gorringe, K.L., 2001. Loss of Heterozygosity. eLS. John Wiley Sons, Ltd.
Greenberg, P.L., Stone, R.M., Al-Kali, A., Barta, S.K., Bejar, R., Bennett, J.M., et al., 2017. Myelodysplastic syndromes, version 2.2017, NCCN clinical practice guidelines in oncology. J Natl Compr Canc Netw 15 (1), 60–87.
Grimwade, D., Walker, H., Oliver, F., Wheatley, K., Harrison, C., Harrison, G., et al., 1998. The importance of diagnostic cytogenetics on outcome in AML: analysis of 1,612 patients entered into the MRC AML 10 trial. Blood 92 (7), 2322–2333.
Grossmann, V., Kohlmann, A., Zenger, M., Schindela, S., Eder, C., Weissmann, S., et al., 2011. A deep-sequencing study of chronic myeloid leukemia patients in blast crisis (BC-CML) detects mutations in 76.9% of cases. Leukemia 25, 557.
Hallek, M., Cheson, B.D., Catovsky, D., Caligaris-Cappio, F., Dighiero, G., Dohner, H., et al., 2008. Guidelines for the diagnosis and treatment of chronic lymphocytic leukemia: a report from the International workshop on chronic lymphocytic leukemia (IWCLL) updating the national cancer institute-working group (NCI-WG) 1996 guidelines. Blood.
Harrison, C.J., 2015. Spotlight on iAMP21 acute lymphoblastic leukemia (ALL), a high-risk pediatric disease. Blood 125 (9), 1383–1386.
Harrison, C.J., Haas, O., Harbott, J., Biondi, A., Stanulla, M., Trka, J., et al., 2010. Detection of prognostically relevant genetic abnormalities in childhood B-cell precursor acute lymphoblastic leukaemia: recommendations from the biology and diagnosis committee of the International Berlin-frankfürt-münster study group. Br. J. Haematol. 151 (2), 132–142.
Harrison, C.J., Moorman, A.V., Barber, K.E., Broadfield, Z.J., Cheung, K.L., Harris, R.L., et al., 2005. Interphase molecular cytogenetic screening for chromosomal abnormalities of prognostic significance in childhood acute lymphoblastic leukaemia: a UK cancer cytogenetics group study. Br. J. Haematol. 129 (4), 520–530.
Harrison, C.J., Moorman, A.V., Schwab, C., Carroll, A.J., Raetz, E.A., Devidas, M., et al., 2014. An international study of intrachromosomal amplification of chromosome 21 (iAMP21): cytogenetic characterization and outcome. Leukemia 28 (5), 1015–1021.
Hay, D., Hatton, C.S.R., Weatherall, D.J., 2017. The future of academic haematology. Br. J. Haematol. 176 (5), 721–727.
He, J., Abdel-Wahab, O., Nahas, M.K., Wang, K., Rampal, R.K., Intlekofer, A.M., et al., 2016. Integrated genomic DNA/RNA profiling of hematologic malignancies in the clinical setting. Blood.
Heerema, N.A., Carroll, A.J., Devidas, M., Loh, M.L., Borowitz, M.J., Gastier-Foster, J.M., et al., 2013. Intrachromosomal amplification of chromosome 21 Is associated with inferior outcomes in children with acute lymphoblastic leukemia treated in contemporary standard-risk children's oncology group studies: a report from the children's oncology group. J. Clinical Oncol. 31 (27), 3397–3402.
Heim, S.M.F., 2015. Cancer Cytogenetics: Chromosomal and Molecular Genetic Aberrations of Tumor Cells. John Wiley & Sons.
Hodge, J.C., Kanagal-Shamanna, R., Xu, X., Bryke, C., Dash, D.P., Dixon-Mciver, A., et al., 2017. Genomic copy number aberrations and copy neutral loss of heterozygosity evaluation in myeloid neoplasms: evidence-based recommendations for clinical genetic testing from the myeloid malignancies working group of the cancer genomics consortium. Cancer Genetics 214, 37.
Hoelzer, D., Bassan, R., Dombret, H., Fielding, A., Ribera, J.M., Buske, C., et al., 2016. Acute lymphoblastic leukaemia in adult patients: ESMO clinical practice guidelines for diagnosis, treatment and follow-up. Ann. Oncol. 27 (suppl 5), v69–v82.
Holland, A.J., Cleveland, D.W., 2012. Chromoanagenesis and cancer: mechanisms and consequences of localized, complex chromosomal rearrangements. Nat. Med. 18 (11), 1630–1638.
Hunger, S.P., Mullighan, C.G., 2015. Redefining ALL classification: toward detecting high-risk ALL and implementing precision medicine. Blood.
Jäger, R., Gisslinger, H., Passamonti, F., Rumi, E., Berg, T., Gisslinger, B., et al., 2010. Deletions of the transcription factor ikaros in myeloproliferative neoplasms. Leukemia 24, 1290.
Jeffries, S., Trim, N., Huxley, E., Ford, L., Raghavan, M., Soden, J., et al., 2015. Genetic analysis using a High density SNP array in myelodysplastic syndrome: clinical utility and comparative analysis study compared to metaphase chromosome analysis. Blood 126 (23) 5259-5259.
Jenkinson, S., Kirkwood, A.A., Goulden, N., Vora, A., Linch, D.C., Gale, R.E., 2016. Impact of PTEN abnormalities on outcome in pediatric patients with T-cell acute lymphoblastic leukemia treated on the MRC UKALL2003 trial. Leukemia 30 (1), 39–47.
Jennings, L.J., Arcila, M.E., Corless, C., Kamel-Reid, S., Lubin, I.M., Pfeifer, J., et al., 2017. Guidelines for validation of next-generation sequencing-based oncology panels: a joint consensus recommendation of the association for molecular pathology and College of American pathologists. J. Mol. Diagn. 19 (3), 341–365.
Jerez, A., Sugimoto, Y., Makishima, H., Verma, A., Jankowska, A.M., Przychodzen, B., et al., 2012. Loss of heterozygosity in 7q myeloid disorders: clinical associations and genomic pathogenesis. Blood 119 (25), 6109–6117.
Jones, M.J., Jallepalli, P.V., 2012. Chromothripsis: chromosomes in crisis. Dev. Cell 23 (5), 908–917.
Juliusson, G., Oscier, D.G., Fitchett, M., Ross, F.M., Stockdill, G., Mackie, M.J., et al., 1990. Prognostic subgroups in B-cell chronic lymphocytic leukemia defined by specific chromosomal abnormalities. N. Engl. J. Med. 323 (11), 720–724.
Kadia, T.M., Jain, P., Ravandi, F., Garcia-Manero, G., Andreef, M., Takahashi, K., et al., 2016. TP53 mutations in newly diagnosed acute myeloid leukemia: clinicomolecular

characteristics, response to therapy, and outcomes. Cancer 122 (22), 3484–3491.
Kanagal-Shamanna, R., Singh, R.R., Routbort, M.J., Patel, K.P., Medeiros, L.J., Luthra, R., 2016. Principles of analytical validation of next-generation sequencing based mutational analysis for hematologic neoplasms in a CLIA-certified laboratory. Expert Rev. Mol. Diagn. 16 (4), 461–472.
Kawamata, N., Ogawa, S., Zimmermann, M., Niebuhr, B., Stocking, C., Sanada, M., et al., 2008. Cloning of genes involved in chromosomal translocations by high-resolution single nucleotide polymorphism genomic microarray. Proc. Natl. Acad. Sci. U. S. A. 105 (33), 11921–11926.
Kim, T.M., Xi, R., Luquette, L.J., Park, R.W., Johnson, M.D., Park, P.J., 2013. Functional genomic analysis of chromosomal aberrations in a compendium of 8000 cancer genomes. Genome Res. 23 (2), 217–227.
Kloosterman, W.P., Cuppen, E., 2013. Chromothripsis in congenital disorders and cancer: similarities and differences. Curr. Opin. Cell Biol. 25 (3), 341–348.
Kloosterman, W.P., Koster, J., Molenaar, J.J., 2014. Prevalence and clinical implications of chromothripsis in cancer genomes. Curr Opin Oncol 26 (1), 64–72.
Krauss, S., Sokal, J.E., Sandberg, A.A., 1964. COmparison of philadelphia chromosome-positive and -negative patients with chronic myelocytic leukemia. Ann. Intern. Med. 61 (4), 625–635.
Krönke, J., Kuchenbauer, F., Kull, M., Teleanu, V., Bullinger, L., Bunjes, D., et al., 2016. IKZF1 expression is a prognostic marker in newly diagnosed standard-risk multiple myeloma treated with lenalidomide and intensive chemotherapy: a study of the German myeloma study group (DSMM). Leukemia 31, 1363.
L'Abbate, A., Tolomeo, D., Cifola, I., Severgnini, M., Turchiano, A., Augello, B., et al., 2018. MYC-containing amplicons in acute myeloid leukemia: genomic structures, evolution, and transcriptional consequences. Leukemia 32 (10), 2152–2166.
Levsky, J.M., Singer, R.H., 2003. Fluorescence in situ hybridization: past, present and future. J. Cell Sci. 116 (Pt 14), 2833–2838.
Liu, G., Stevens, J.B., Horne, S.D., Abdallah, B.Y., Ye, K.J., Bremer, S.W., et al., 2014. Genome chaos: survival strategy during crisis. Cell Cycle 13 (4), 528–537.
Maciejewski, J.P., Tiu, R.V., O'Keefe, C., 2009. Application of array-based whole genome scanning technologies as a cytogenetic tool in haematological malignancies. Br. J. Haematol. 146 (5), 479–488.
Magrangeas, F., Avet-Loiseau, H., Munshi, N.C., Minvielle, S., 2011. Chromothripsis identifies a rare and aggressive entity among newly diagnosed multiple myeloma patients. Blood 118 (3), 675–678.
Makishima, H., Yoshizato, T., Nannya, Y., Momozawa, Y., Atsuta, Y., Shiozawa, Y., et al., 2018. Novel and significant impact of germline variants predisposed to pathogenic somatic mutations and loss of heterozygosity (LOH) in myelodysplastic syndromes (MDS) and clonal hematopoiesis of indeterminate potential (CHIP). Blood 132 (Suppl 1) 108-108.
Malhotra, A., Lindberg, M., Faust, G.G., Leibowitz, M.L., Clark, R.A., Layer, R.M., et al., 2013. Breakpoint profiling of 64 cancer genomes reveals numerous complex rearrangements spawned by homology-independent mechanisms. Genome Res. 23 (5), 762–776.
Mallo, M., Arenillas, L., Espinet, B., Salido, M., Hernandez, J.M., Lumbreras, E., et al., 2008. Fluorescence in situ hybridization improves the detection of 5q31 deletion in myelodysplastic syndromes without cytogenetic evidence of 5q. Haematologica 93 (7), 1001–1008.
Martinez, P., Kimberley, C., BirkBak, N.J., Marquard, A., Szallasi, Z., Graham, T.A., 2017. Quantification of within-sample genetic heterogeneity from SNP-array data. Sci. Rep. 7, 3248.
McEvoy, J., Nagahawatte, P., Finkelstein, D., Richards-Yutz, J., Valentine, M., Ma, J., et al., 2014. RB1 gene inactivation by chromothripsis in human retinoblastoma. Oncotarget.
McGowan-Jordan, J., Simons, A., Schmid, M., 2016. ISCN 2016: An International System for Human Cytogenetic Nomenclature. S. Karger, AG, Basel (Switzerland).
Medeiros, B.C., Othus, M., Estey, E.H., Fang, M., Appelbaum, F.R., 2014. Unsuccessful diagnostic cytogenetic analysis is a poor prognostic feature in acute myeloid leukaemia. Br. J. Haematol. 164 (2), 245–250.
Meijerink, J.P., den Boer, M.L., Pieters, R., 2009. New genetic abnormalities and treatment response in acute lymphoblastic leukemia. " Semin Hematol 46 (1), 16–23.
Mikhail, F.M., Heerema, N.A., Rao, K.W., Burnside, R.D., Cherry, A.M., Cooley, L.D., 2016. Section E6.1–6.4 of the ACMG technical standards and guidelines: chromosome studies of neoplastic blood and bone marrow–acquired chromosomal abnormalities. Genet. Med. 18, 635.
Miron, P.M., Wenger, G.D., Chaubey, A., 2017. 18 - CGC working group recommendations for CLL: utility of molecular technologies such as microarrays and NGS for routine diagnostic use. Cancer Genetics 214-215, 37–38.
Mitchell, J.S., Li, N., Weinhold, N., Försti, A., Ali, M., van Duin, M., et al., 2016. Genome-wide association study identifies multiple susceptibility loci for multiple myeloma. Nat. Commun. 7, 12050.
Moorman, A.V., Enshaei, A., Schwab, C., Wade, R., Chilton, L., Elliott, A., et al., 2014. A novel integrated cytogenetic and genomic classification refines risk stratification in pediatric acute lymphoblastic leukemia. Blood 124 (9), 1434–1444.
Mrózek, K., Heerema, N.A., Bloomfield, C.D., 2004. Cytogenetics in acute leukemia. Blood Rev. 18 (2), 115–136.
Mukherjee, S., Sathanoori, M., Ma, Z., Andreatta, M., Lennon, P.A., Wheeler, S.R., et al., 2017. Addition of chromosomal microarray and next generation sequencing to FISH and classical cytogenetics enhances genomic profiling of myeloid malignancies. Cancer Genetics 216–217, 128–141.
Mullighan, C.G., 2012. Molecular genetics of B-precursor acute lymphoblastic leukemia. J. Clinical Invest. 122 (10), 3407–3415.
Munshi, N.C., Anderson, K.C., Bergsagel, P.L., Shaughnessy, J., Palumbo, A., Durie, B., et al., 2011a. consensus recommendations for risk stratification in multiple myeloma: report of the International myeloma workshop consensus panel 2. Blood 117 (18), 4696–4700.
Munshi, N.C., Anderson, K.C., Bergsagel, P.L., Shaughnessy, J., Palumbo, A., Durie, B., et al., 2011b. Guidelines for risk stratification in multiple myeloma: report of the International myeloma workshop consensus panel 2. Blood.
Nahi, H., Sutlu, T., Jansson, M., Alici, E., Gahrton, G., 2011. Clinical impact of chromosomal aberrations in multiple myeloma. J. Intern. Med. 269 (2), 137–147.
Nordgren, A., Heyman, M., Sahlen, S., Schoumans, J., Soderhall, S., Nordenskjold, M., et al., 2002. Spectral karyotyping and interphase FISH reveal abnormalities not detected by conventional G-banding. Implications for treatment stratification of childhood acute lymphoblastic leukaemia: detailed analysis of 70 cases. Eur. J. Haematol. 68 (1), 31–41.
Nowak, D., Ogawa, S., Muschen, M., Kato, M., Kawamata, N., Meixel, A., et al., 2010. SNP array analysis of tyrosine kinase inhibitor-resistant chronic myeloid leukemia identifies heterogeneous secondary genomic alterations. Blood 115 (5), 1049–1053.
Nowell, P.C., 2007. Discovery of the philadelphia chromosome: a personal perspective. J. Clin. Invest. 117 (8), 2033–2035.
Ogawa, S., 2019. Genetics of MDS. Blood 133 (10), 1049–1059.
Ohshima, K., Hatakeyama, K., Nagashima, T., Watanabe, Y., Kanto, K., Doi, Y., et al., 2017. Integrated analysis of gene expression and copy number identified potential cancer driver genes with amplification-dependent overexpression in 1,454 solid tumors. Sci. Rep. 7 (1), 641.
Olsson, L., Zettermark, S., Biloglav, A., Castor, A., Behrendtz, M., Forestier, E., et al., 2016. The genetic landscape of paediatric de novo acute myeloid leukaemia as defined by single nucleotide polymorphism array and exon sequencing of 100 candidate genes. Br. J. Haematol. 174 (2), 292–301.
Palumbo, A., Avet-Loiseau, H., Oliva, S., Lokhorst, H.M., Goldschmidt, H., Rosinol, L., et al., 2015. Revised International staging system for multiple myeloma: a report from International myeloma working group. J. Clin. Oncol.
Papaemmanuil, E., Gerstung, M., Bullinger, L., Gaidzik, V.I., Paschka, P., Roberts, N.D., et al., 2016. Genomic classification and prognosis in acute myeloid leukemia. N. Engl. J. Med. 374 (23), 2209–2221.
Papenhausen, P.R., Griffin, S., Tepperberg, J., 2005. Oncogene amplification in transforming myelodysplasia. Exp. Mol. Pathol. 79 (2), 168–175.
Paskulin, D.D., Giacomazzi, J., Nakachi, I., Varella-Garcia, M., Ashton-Prolla, P., 2014. High-density SNP array analysis of TP53 p.R337H mutation carriers. J. Clin. Oncol. 32 (15_suppl) e12500-e12500.
Peterson, J.F., Van Dyke, D.L., Hoppman, N.L., Kearney, H.M., Sukov, W.R., Greipp, P.T., et al., 2018. The utilization of chromosomal microarray technologies for hematologic NeoplasmsAn ACLPS critical review. Am. J. Clin. Pathol. 150 (5), 375–384.
Poulain, S., Roumier, C., Galiègue-Zouitina, S., Daudignon, A., Herbaux, C., Aiijou, R., et al., 2013. Genome wide SNP array identified multiple mechanisms of genetic changes in waldenstrom macroglobulinemia. Am. J. Hematol. 88 (11), 948–954.
Pui, C.H., Evans, W.E., 2013. A 50-year journey to cure childhood acute lymphoblastic leukemia. Semin Hematol 50 (3), 185–196.
Pui, C.H., Mullighan, C.G., Evans, W.E., Relling, M.V., 2012. Pediatric acute lymphoblastic leukemia: where are we going and how do we get there? Blood 120 (6), 1165–1174.
Raca, G., Biegel, J., Cooley, L., Dubuc, A., Hirsch, B., Horner, V., et al., 2017. 15 - classifying and reporting acquired copy number variants (CNVs) and copy neutral loss of heterozygosity (CN-LOH) in neoplastic disorders: joint recommendations from the American College of medical genetics and genomics (ACMG), and the cancer genomics consortium (CGC). Cancer Genetics 214-215, 36–37.
Rack, K.A., van den Berg, E., Haferlach, C., Beverloo, H.B., Costa, D., Espinet, B., et al., 2019. European Recommendations and Quality Assurance for Cytogenomic Analysis of Haematological Neoplasms. Leukemia.
Renneville, A., Abdelali, R.B., Chevret, S., Nibourel, O., Cheok, M., Pautas, C., et al., 2014. Clinical impact of gene mutations and lesions detected by SNP-array karyotyping in acute myeloid leukemia patients in the context of gemtuzumab ozogamicin treatment: results of the ALFA-0701 trial. Oncotarget 5 (4), 916–932.
Reshmi, S.C., Harvey, R.C., Roberts, K.G., Stonerock, E., Smith, A., Jenkins, H., et al., 2017. Targetable kinase gene fusions in high risk B-ALL: a study from the children's oncology group. Blood.
Righolt, C., Mai, S., 2012. Shattered and stitched chromosomes-chromothripsis and chromoanasynthesis-manifestations of a new chromosome crisis? Genes. Chromosomes Cancer 51 (11), 975–981.
Roberts, K.G., Mullighan, C.G., 2015. Genomics in acute lymphoblastic leukaemia: insights and treatment implications. Nat Rev Clin Oncol 12 (6), 344–357.
Roberts, K.G., Reshmi, S.C., Harvey, R.C., Chen, I.-M., Patel, K., Stonerock, E., et al., 2018. Genomic and outcome analyses of Ph-like ALL in NCI standard-risk patients: a report from the children's oncology group. Blood 132 (8), 815–824.
Rode, A., Maass, K.K., Willmund, K.V., Lichter, P., Ernst, A., 2016. Chromothripsis in cancer cells: an update. Int. J. Cancer 138 (10), 2322–2333.
Rossi, A., Voigtlaender, M., Janjetovic, S., Thiele, B., Alawi, M., März, M., et al., 2017. Mutational landscape reflects the biological continuum of plasma cell dyscrasias. Blood Cancer J. 7 (2), e537.
Safavi, S., Olsson, L., Biloglav, A., Veerla, S., Blendberg, M., Tayebwa, J., et al., 2015. Genetic and epigenetic characterization of hypodiploid acute lymphoblastic leukemia. Oncotarget 6 (40), 42793–42802.
Sawyer, J.R., 2011. The prognostic significance of cytogenetics and molecular profiling in multiple myeloma. Cancer Genet 204 (1), 3–12.
Schlenk, R.F., Döhner, K., Krauter, J., Fröhling, S., Corbacioglu, A., Bullinger, L., et al., 2008. Mutations and treatment outcome in cytogenetically Normal acute myeloid leukemia. N. Engl. J. Med. 358 (18), 1909–1918.
Schoumans, J., Suela, J., Hastings, R., Muehlematter, D., Rack, K., van den Berg, E., et al., 2016. Guidelines for genomic array analysis in acquired haematological neoplastic disorders. Genes. Chromosomes Cancer 55 (5), 480–491.

Schwab, C., Ryan, S.L., Chilton, L., Elliott, A., Murray, J., Richardson, S., et al., 2016. EBF1-PDGFRB fusion in pediatric B-cell precursor acute lymphoblastic leukemia (BCP-ALL): genetic profile and clinical implications. Blood 127 (18), 2214–2218.
Shaffer, L.G., 2005. American College of medical genetics guideline on the cytogenetic evaluation of the individual with developmental delay or mental retardation. Genet. Med. 7, 650.
Shao, L., Kang, S.H., Li, J., Hixson, P., Taylor, J., Yatsenko, S.A., et al., 2010. Array comparative genomic hybridization detects chromosomal abnormalities in hematological cancers that are not detected by conventional cytogenetics. J. Mol. Diagn. 12 (5), 670–679.
Shen, W., Szankasi, P., Sederberg, M., Schumacher, J., Frizzell, K., Gee, E.P., et al., 2015. Targeted detection of copy number variants using a myeloid malignancy next generation sequencing mutation panel allows comprehensive genetic analysis using a single testing method. Blood 126 (23) 2887-2887.
Simons, A., Sikkema-Raddatz, B., de Leeuw, N., Konrad, N.C., Hastings, R.J., Schoumans, J., 2012. Genome-wide arrays in routine diagnostics of hematological malignancies. Hum. Mutat. 33 (6), 941–948.
Slovak, M.L., Smith, D.D., Bedell, V., Hsu, Y.H., O'Donnell, M., Forman, S.J., et al., 2010. Assessing karyotype precision by microarray-based comparative genomic hybridization in the myelodysplastic/myeloproliferative syndromes. Mol Cytogenet 3, 23.
South, S.T., Lee, C., Lamb, A.N., Higgins, A.W., Kearney, H.M., 2013. ACMG standards and guidelines for constitutional cytogenomic microarray analysis, including postnatal and prenatal applications: revision 2013. Genet. Med. 15, 901.
Soverini, S., de Benedittis, C., Mancini, M., Martinelli, G., 2015. Mutations in the BCR-ABL1 kinase domain and elsewhere in chronic myeloid leukemia. Clinical Lymphoma Myeloma and Leukemia 15, S120–S128.
Speicher, M.R., Ballard, S.G., Ward, D.C., 1996. Karyotyping human chromosomes by combinatorial multi-fluor FISH. Nat. Genet. 12, 368.
Stanulla, M., Dagdan, E., Zaliova, M., Moricke, A., Palmi, C., Cazzaniga, G., et al., 2018. IKZF1(plus) defines a New minimal residual disease-dependent very-poor prognostic profile in pediatric B-cell precursor acute lymphoblastic leukemia. J. Clin. Oncol. 36 (12), 1240–1249.
Stephens, P.J., Greenman, C.D., Fu, B., Yang, F., Bignell, G.R., Mudie, L.J., et al., 2011. Massive genomic rearrangement acquired in a single catastrophic event during cancer development. Cell 144 (1), 27–40.
Stevens-Kroef, M., Simons, A., Rack, K., Hastings, R.J., 2017. Cytogenetic nomenclature and reporting. Cancer Cytogenetics: Methods and Protocols 303–309.
Stevens-Kroef, M., Weghuis, D.O., Croockewit, S., Derksen, L., Hooijer, J., ElIdrissi-Zaynoun, N., et al., 2012. High detection rate of clinically relevant genomic abnormalities in plasma cells enriched from patients with multiple myeloma. Genes. Chromosomes Cancer 51 (11), 997–1006.
Surrey, L.F., Luo, M., Chang, F., Li, M.M., 2016. The genomic era of clinical oncology: integrated genomic analysis for precision cancer care. Cytogenet. Genome Res. 150 (3-4), 162–175.
Sutton, R., Venn, N.C., Law, T., Boer, J.M., Trahair, T.N., Ng, A., et al., 2018. A risk score including microdeletions improves relapse prediction for standard and medium risk precursor B-cell acute lymphoblastic leukaemia in children. Br. J. Haematol. 180 (4), 550–562.
Swerdlow, S.H., Campo, E., Harris, N.L., Jaffe, E.S., Pileri, S.A., Stein, H., et al., 2017. WHO Classification of Tumours of Haematopoietic and Lymphoid Tissues. IARC, Lyon, France.
Tang, G., DiNardo, C., Zhang, L., Ravandi, F., Khoury, J.D., Huh, Y.O., et al., 2015. MLL gene amplification in acute myeloid leukemia and myelodysplastic syndromes is associated with characteristic clinicopathological findings and TP53 gene mutation. Hum. Pathol. 46 (1), 65–73.
Tiu, R.V., Gondek, L.P., O'Keefe, C.L., Elson, P., Huh, J., Mohamedali, A., et al., 2011. Prognostic impact of SNP array karyotyping in myelodysplastic syndromes and related myeloid malignancies. Blood.
Trakadis, Y.S., Michael, 2011. Microarray as a first genetic test in global developmental delay: a cost-effectiveness analysis. Developmental Medicine & Child Neurology 53 (11), 994–999.
Trask, B.J., 2002. Human cytogenetics: 46 chromosomes, 46 years and counting. Nat. Rev. Genet. 3, 769.
Tsao, L., Draoua, H.Y., Osunkwo, I., Nandula, S.V., Murty, V.V.S., Mansukhani, M., et al., 2004. Mature B-cell acute lymphoblastic leukemia with t(9;11) translocation: a distinct subset of B-cell acute lymphoblastic leukemia. Mod. Pathol. 17 (7), 832–839.
Van Vlierberghe, P., Ferrando, A., 2012. The molecular basis of T cell acute lymphoblastic leukemia. J. Clin. Invest. 122 (10), 3398–3406.
Veigaard, C., Norgaard, J.M., Kjeldsen, E., 2011. Genomic profiling in high hyperdiploid acute myeloid leukemia: a retrospective study of 19 cases. Cancer Genet 204 (9), 516–521.
Vijayakrishnan, J., Studd, J., Broderick, P., Kinnersley, B., Holroyd, A., Law, P.J., et al., 2018. Genome-wide association study identifies susceptibility loci for B-cell childhood acute lymphoblastic leukemia. Nat. Commun. 9 (1), 1340.
Wan, J.C.M., Massie, C., Garcia-Corbacho, J., Mouliere, F., Brenton, J.D., Caldas, C., et al., 2017. Liquid biopsies come of age: towards implementation of circulating tumour DNA. Nat. Rev. Cancer 17, 223.
Cancer cytogenetics methods and protocols. In: Wan, T.S.K. (Ed.), Methods in Molecular Biology. Springer, New York.
Wang, Y., Miller, S., Roulston, D., Bixby, D., Shao, L., 2016. Genome-Wide single-nucleotide polymorphism array analysis improves prognostication of acute lymphoblastic Leukemia/Lymphoma. J. Mol. Diagn.
Whang, J., Frei, E., Tjio, J.H., Carbone, P.P., Brecher, G., 1963. The distribution of the philadelphia chromosome in patients with chronic myelogenous leukemia. Blood 22 (6), 664.
Whitman, S.P., Liu, S., Vukosavljevic, T., Rush, L.J., Yu, L., Liu, C., et al., 2005. The MLL partial tandem duplication: evidence for recessive gain-of-function in acute myeloid leukemia identifies a novel patient subgroup for molecular-targeted therapy. Blood 106 (1), 345–352.
Wolff, D.J., Bagg, A., Cooley, L.D., Dewald, G.W., Hirsch, B.A., Jacky, P.B., et al., 2007. Guidance for fluorescence in situ hybridization testing in hematologic disorders. J. Mol. Diagnostics 9 (2), 134–143.
Xu, X., Johnson, E.B., Leverton, L., Arthur, A., Watson, Q., Chang, F.L., et al., 2013. The advantage of using SNP array in clinical testing for hematological malignancies–a comparative study of three genetic testing methods. Cancer Genet 206 (9-10), 317–326.
Yang, J.J., Cheng, C., Devidas, M., Cao, X., Fan, Y., Campana, D., et al., 2011. Ancestry and pharmacogenomics of relapse in acute lymphoblastic leukemia. Nat. Genet. 43 (3), 237–241.
Yang, J.J., Cheng, C., Yang, W., Pei, D., Cao, X., Fan, Y., et al., 2009. Genome-wide interrogation of germline genetic variation associated with treatment response in childhood acute lymphoblastic leukemia. JAMA 301 (4), 393–403.
Yasar, D., Karadogan, I., Alanoglu, G., Akkaya, B., Luleci, G., Salim, O., et al., 2010. Array comparative genomic hybridization analysis of adult acute leukemia patients. Cancer Genet. Cytogenet. 197 (2), 122–129.
Young, B.D., Debernardi, S., Lillington, D.M., Skoulakis, S., Chaplin, T., Foot, N.J., et al., 2006. A role for mitotic recombination in leukemogenesis. Adv. Enzyme Regul. 46, 90–97.
Zhan, F., Sawyer, J., Tricot, G., 2006. The role of cytogenetics in myeloma. Leukemia 20 (9), 1484–1486.
Zhang, C.Z., Leibowitz, M.L., Pellman, D., 2013. Chromothripsis and beyond: rapid genome evolution from complex chromosomal rearrangements. Genes Dev. 27 (23), 2513–2530.
Zhang, J., Ding, L., Holmfeldt, L., Wu, G., Heatley, S.L., Payne-Turner, D., et al., 2012. The genetic basis of early T-cell precursor acute lymphoblastic leukaemia. Nature 481 (7380), 157–163.