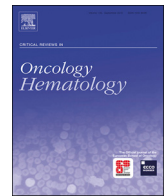




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Clinical use of SNP-microarrays for the detection of genome-wide changes in haematological malignancies

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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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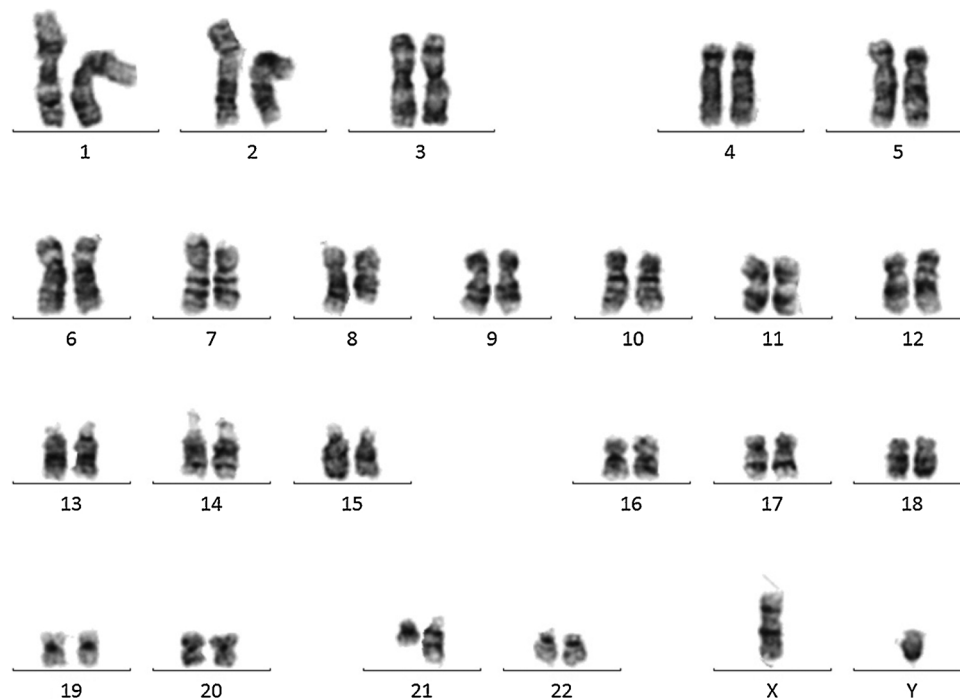


Fig. 1. A G-banded karyotype, showing a $t(8;21)(q22;q22)$, is a standard cytogenetic tool for investigation of haematological malignancies.

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 (Juliussen, 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; Vijaykrishnan, 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 mechanism 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 than 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 tandem 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-PDGFRB* 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 cytogenetic 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 chromoanasythesis (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 chromoanasythesis 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, chromoanasythesis 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 chromoanasythesis exhibit uniquely identifiable genomic signatures on SNP-microarray that enable their detection in one simple assay (Fig. 4).

The instability of a cell can initiate 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

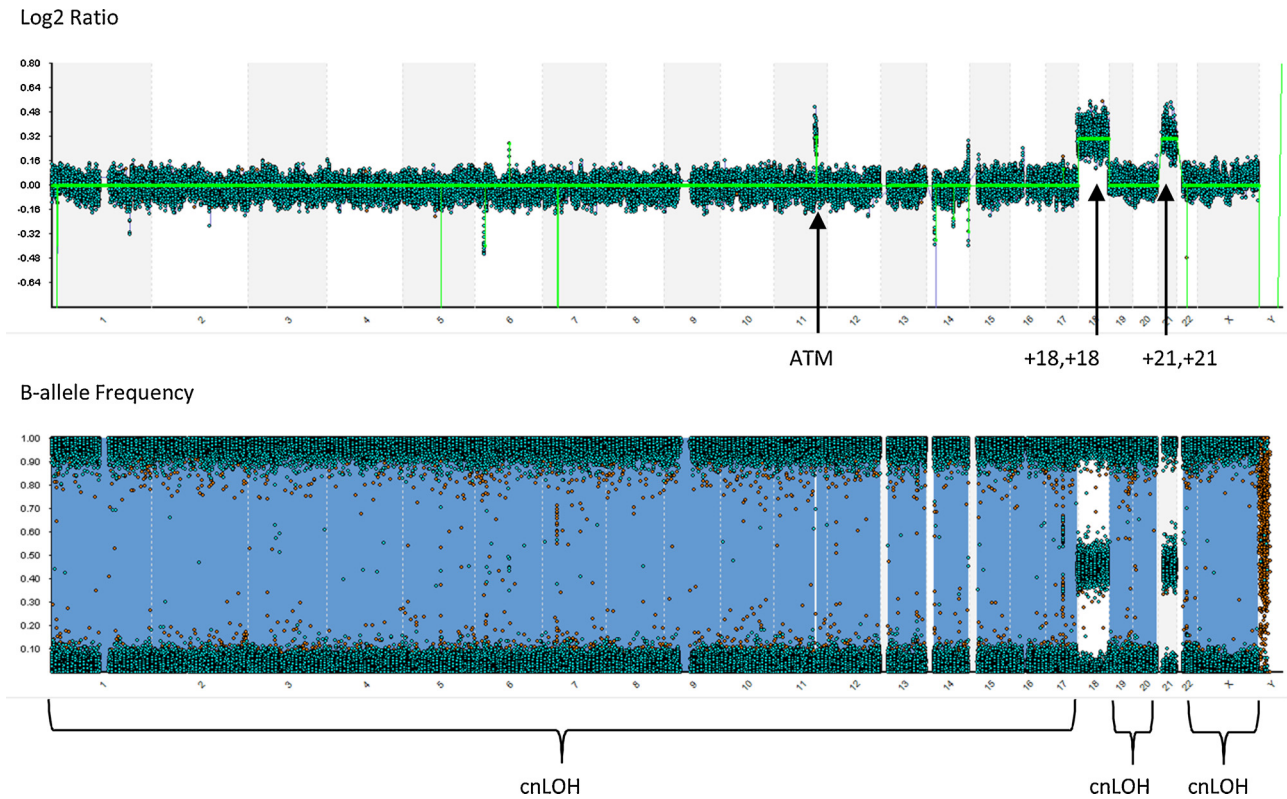


Fig. 2. Whole genome view from a SNP-microarray performed on the diagnostic bone marrow specimen submitted for investigation of ALL. Top plot shows the log2 ratio achieved across the genome and indicates two additional copies of 11q22.3 and whole chromosomes 18 and 21. The B-allele frequency plot (lower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

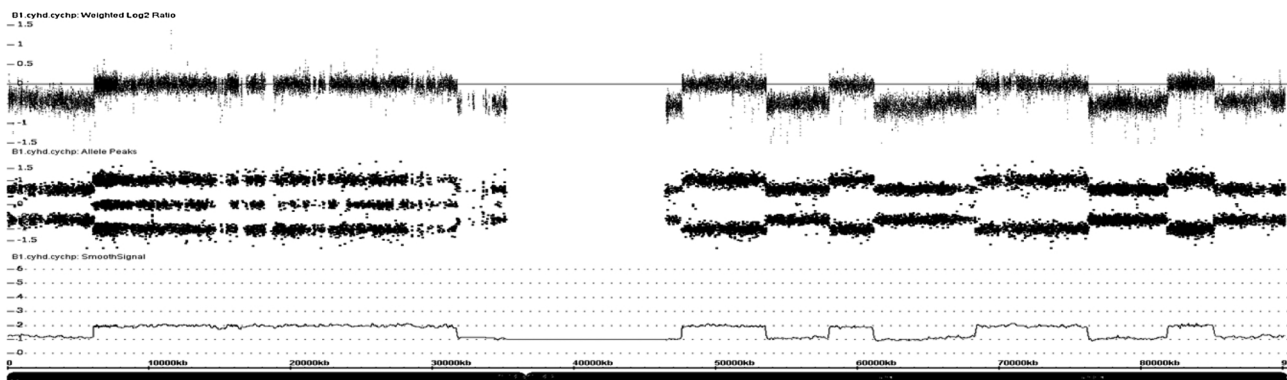


Fig. 3. Chromothripsis identified by SNP-microarray on chromosome 16 in multiple myeloma (Berry, Dixon-McIver et al. 2017).

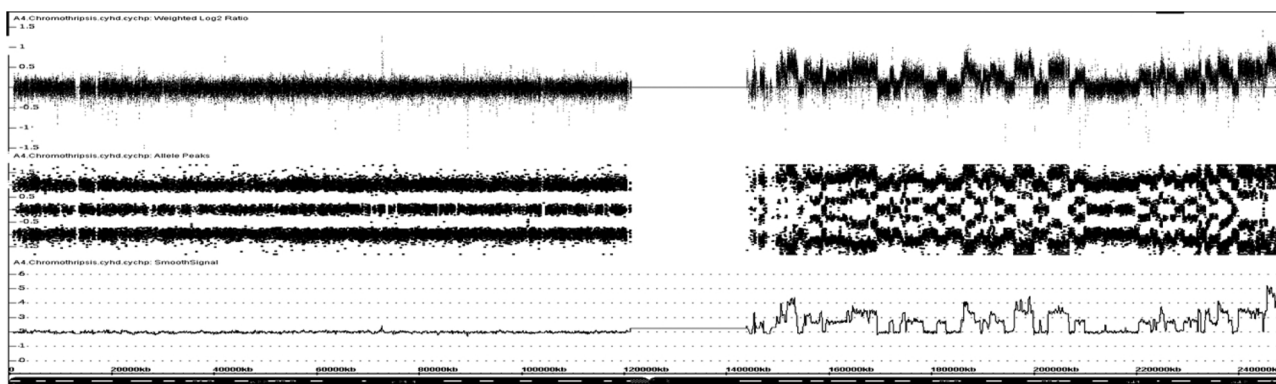


Fig. 4. Chromoanaphythesis identified by SNP-microarray on chromosome 1q in multiple myeloma (Berry, Dixon-McIver et al. 2017).

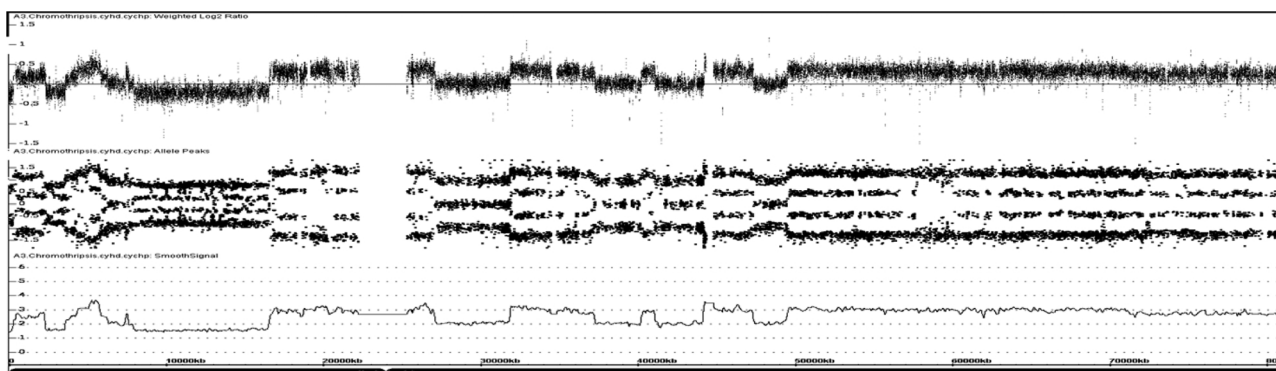


Fig. 5. A combination of a complex step-wise event and chromoanaphythesis identified by SNP-microarray (Berry, Dixon-McIver et al. 2017).

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.

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