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The importance of cytogenetic and molecular aberrations in multiple myeloma

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Abstract

Multiple myeloma (MM) is a heterogeneous clonal malignancy of plasma cells characterized by cytogenetic and molecular abnormalities. Chromosomal abnormalities are present at diagnosis and can evolve during the progression of MM. Metaphase karyotyping and fluorescence *in situ* hybridization are considered the standard diagnostic procedures performed in clinical practice. These test results are required to determine the Revised International Staging System classification, treatment algorithms, and short- and long-term prognoses.

Given the dynamic development of cytogenetic and molecular research, we should expect further progress in better understanding the biology of MM and changes to patient care in the coming years.

Key words: cytogenetic abnormalities, multiple myeloma, prognosis, risk classifications

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Introduction

Multiple myeloma (MM) is a heterogeneous clonal malignancy of plasma cells (PCs) that accounts for 1.8% of all cancers, and about 10–15% of all hematological malignancies [1]. The incidence in Europe is 4.5–6.0/100,000/year. The median age at diagnosis is 70 years, and 35% of patients are older than 75 [1, 2]. According to Narodowy Fundusz Zdrowia data, in 2016 there were nearly 2,600 new MM cases in Poland [3].

Multiple myeloma is characterized by chromosomal instability and cytogenetic abnormalities (CA) with significant impacts on prognosis [4–6]. Using current technology, abnormal karyotypes are found in c.20–30% of MM cases, and more often in advanced stages of MM [7, 8]. The use of the fluorescence *in situ* hybridization (FISH) technique reveals chromosomal aberrations in over 80% of cases [9].

Based on multicenter studies, the most common, clinically significant, CA detected in neoplastic plasma cells have been determined, and this is reflected in the new risk-stratification algorithm of MM, the Revised International Staging System (R-ISS), which considers the presence of the most common unfavorable CA (Table I) [10]. Less common CAs, such as t(14;20) and gain of chromosome 1q are not included in the R-ISS. This makes other staging systems like the Mayo Clinic Risk Stratification for Multiple Myeloma mSMART 3.0 (Table II) more appropriate in the presence of these CAs [11, 12].

Pathogenesis

The current hypothesis for the development of MM is the evolution of monoclonal gammopathy of undetermined

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Table I. Revised International Staging System (R-ISS) for multiple myeloma [10]

Stage	Criteria
I	$Beta_2$-microglobulin <3.5 mg/dL and albumin ≥3.5 g/dL, and
	Standard-risk CA by iFISH, and
	Normal LDH (defined as lower than ULN)
II	Not R-ISS stage I or III
III	$Beta_2$-microglobulin ≥5.5 mg/dL, and
	Either high-risk CA by iFISH [del(17p) and/or t(4;14) and/or t(14;16)] or
	High LDH (defined as higher than ULN)

CA — chromosomal abnormalities; del — deletion; iFISH — interphase fluorescence *in situ* hybridization; LDH — lactate dehydrogenase; t — translocation; ULN — upper limit of normal

significance (MGUS), which then progresses to smoldering and symptomatic MM. In general, MGUS develops with signs of primary CA. Symptomatic MM then develops as a result of secondary, random CA. The final stage of evolution in genetic changes is extramedullary MM/plasma cell leukemia (PCL) (Figure 1) [13–17].

Diagnostic methods of cytogenetic abnormalities

We recommend that all genetic analyses in MM should be preferentially performed in plasma cells-enriched samples, typically CD38+ and CD138+. Otherwise, samples may be impossible to interpret or give false negatives due to decreased sensitivity [18].

Conventional karyotyping

Karyotyping reveals CA in 20–30% of patients. This method fails to detect several translocations, including t(4;14). Normal karyotype in patients with low proliferation index corresponds to the kinetics of normal BM cells. The use of more sensitive techniques reveals CA in almost all MM [19].

Fluorescence *in situ* hybridization

Fluorescence *in situ* hybridization is currently the standard technique for CA analysis, and is a practical cytogenetic tool to detect genomic aberration *in situ* and enumerate the percentage of cells harboring such abnormalities. It does not detect single-nucleotide variants [17]. Fluorescence *in situ* hybridization testing includes gain of (1q), del(1p), t(4;14)(p16;q32), t(14;16)(q32;q23), del(17p13), t(14;20) and a marker for aneuploidy.

There are three distinct groups of patients with *TP53* dysregulation: monoallelic deletion as part of deletion

Table II. Cytogenetic risk group in multiple myeloma according to International Myeloma Working Group [10, 19] and Mayo Clinic Risk Stratification for Multiple Myeloma [12]

International Myeloma Working Group	Mayo Clinic Risk Stratification for Multiple Myeloma (mSMART)
High-risk	
t(4;14)	t(4;14)
t(14;16)	t(14;16)
t(14;20)	t(14;20)
del17p	del17p
p53 mutation	*p53* mutation
amp1q	Gain 1q
del13p	Double hit MM: any two high-risk genetic abnormalities
Non-hyperdiploidy	Triple hit MM: three or more high-risk genetic abnormalities
Standard-risk	
Others including:	All others including:
• t(11;14)	• trisomies
• t(6;14)	• t(11;14)
	• t(6;14)

t — translocation; amp — amplification; del — deletion; MM — multiple myeloma

of chromosome 17p (~8%); monoallelic mutation (~6%); and biallelic inactivation (~4%). While deletion and biallelic inactivation have poor prognoses, the role of monoallelic mutation is unclear [20]. Table III presents the frequencies of the different abnormalities. For routine diagnosis, testing of t(4;14) and del(17p13) suffices [19].

Singe-nucleotide polymorphism-based mapping arrays

High-resolution genome-wide analysis (GWAS) of single-nucleotide polymorphisms (SNP) detect regions with loss of heterozygosity and numerical abnormalities. SNP mapping arrays identify copy number variations (CNV). Translocations are not usually detected and will require additional FISH. Comparative genomic hybridization is a tool for genome-wide classification of CNVs and detects numerical abnormalities [19].

Gene expression profiling

Gene expression profiling (GEP) is a technique to identify the expression of genes and pathways. Based on RNA expression using microarrays, subgroups of patients are recognized with a unique GEP phenotype that partly corresponds to the TC classification [21]. Developed GEPs

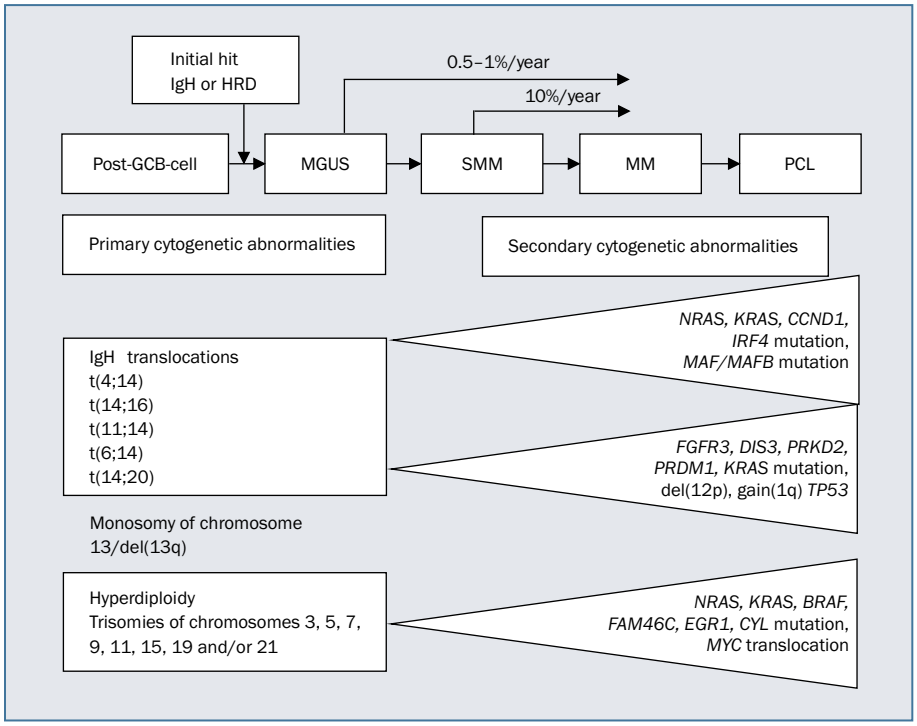

Figure 1. Pathogenesis of multiple myeloma (MM). Primary and secondary cytogenetic abnormalities associated with progression from precursor disease entities such as monoclonal gammopathy of undefined importance (MGUS) and smoldering multiple myeloma (SMM) to MM and plasma cell leukemia (PCL) (modified from Chesi et al. [16] and Manier et al. [17]); IgH — immunoglobulin heavy-chain; HRD — hyperdiploidy; GCB — germinal center B-cell-like; t — translocation; del — deletion

Table III. The most important cytogenetic abnormalities in multiple myeloma, and their prognostic impacts

IgH translocations	Gene(s)	Frequency [%]	Prognostic impact
Primary chromosomal abnormalities			
t(4:14)(p16;q32)	*FGFR3/MMSET*	10–15	Median OS: 5 years
t(6;14)(p21;q32)	*CCND3*	2	Median OS: 7–10 years
t(11;14)(q13;q32)	*CCND1*	15–20	Median OS: 7–10 years
t(14;16)	*C-MAF*	2–5	Median OS: 5 years
t(14;20)(q32;q12)	*MAFB*	1	Median OS: 5 years
Trisomies		40–50	Median OS: 7–10 years
Trisomies plus any one IgH translocation		15	May neutralize HR IgH and del 17p translocations
Hypodiploidy		13–20	Unfavorable prognosis, HR of progression
Deletion/isolated monosomy 13	*RB1, DIS3*	45–50	Effect on prognosis is unclear
Secondary chromosomal abnormalities			
17p deletion	*TP53*	10	Median OS: 5 years
1q21 gain	*CKS1B, ANP32E*	35–40	Median OS: 5 years

IgH — immunoglobulin heavy chain; t — translocation; OS — overall survival; HR — high-risk

highlight an important molecular heterogeneity in multiple myeloma. GEP70 and EMC-92-gene signature have been proved to be useful in risk assessment in clinical trials, and could provide a tool for treatment decision in high-risk MM [22, 23]. High-risk GEP signature is recognized in the mSMART 3.0 risk classification [12].

Cytogenetic risk classifications

According to the International Myeloma Working Group (IMWG), cytogenetic high-risk (HR) MM is identified when there is at least one of the following CA in the FISH test: del17p, t(4;14) or t(14;16) [19]. To the above-mentioned CA

representing a HR MM, researchers from Mayo Clinic have added hypodiploidy and t(14;20). Additionally, ultra-HR, which is defined when >3 CA is found (2%; median overall survival [OS] nine months, Table II), has been identified [24]. These classifications are subject to change as and when new treatments are introduced.

Cytogenetic abnormalities

The CA in MM and their prognostic effects are summarized in Table III [25, 26].

Hyperdiploidy

Depending on the number of chromosomes in the karyotype test, patients with MM can be divided into non-hyperdiploid (NH) and hyperdiploid types. The NH type is characterized by immunoglobulin heavy chain (IgH) translocation associated with a more aggressive MM and shorter survival. The hyperdiploid type is recognized when the number of chromosomes is greater than 46 [27, 28]. The mechanism of hyperdiploidy is not understood. The extra chromosomes are believed to occur in one catastrophic mitosis rather than a gradual increment of chromosomes [17].

The hyperdiploid group accounts for more than half of all MM cases, and the most common evidence is the presence of odd chromosome trisomy [28].

Hyperdiploidy is characterized by increased chromosomal gains, mainly trisomy of chromosomes 3, 5, 7, 9, 11, 15, 19, and 21, and is found in approximately 50% of NDMM patients [29–31]. Hyperdiploidy is defined as the primary CA in MM, and is associated with a favorable outcome. However, the coexistence of hyperdiploidy with unfavorable CA (such as del(17p), t(4;14), and increment 1q) is a negative prognosis factor [32].

Non-hyperdiploidy

The non-hyperdiploid MM group includes hypodiploid (up to 44/45 chromosomes), pseudodiploid (44/45 to 46/47), and near-tetraploid (more than 74) cases. Patients with hypodiploid karyotype present with shorter overall survival (OS). Abnormal clones include hypodiploid, pseudodiploid, or quasi-tetraploid variants, while common translocations are t(11;14) and t(4;14) [14, 33]. Loss of chromosomes 13, 14, 16, and 22 are common in NH MM [29, 32].

IgH translocations

The translocations involving immunoglobulin genes in MM most often concern the heavy chain gene (IgH, 14q32) and are found in 55–80% of patients with MM [24]. IgH translocations are considered to be primary mutations and occur in 50% of patients. They mainly consist of five chromosomal *loci*, 11q13 (15–20% patients), 6p21 (<5% patients), 4p16 (12–15% patients), 16q23 (3% patients), and 20q11 (1% patients), respectively, which contain *CCND1, CCND3, FGFR3/NSD2, MAF* and *MAFB*, respectively [15, 29]. *MYC* translocation is seen in c.15–20% of patients with newly diagnosed (ND) MM, and is considered to be a secondary mutation [30]. Approximately 20% of MM cases harbor mutation in *KRAS* [34].

Translocation t(4;14)(q16;q32)

MM-specific t(4;14)(p16;q32) translocation is detected by FISH or PCR using reverse transcription polymerase chain reaction (RT-PCR) in approximately 10–15% of patients with MM [35]. This translocation increases the expression of two genes: fibroblast growth factor receptor 3 (FGFR3) in 100% of cases; and MM SET (MMSET) in 100% of cases domain genes. In almost 25% of cases, the translocation is unbalanced due to frequent loss of derivative chromosome del(14) and lack of FGFR3 expression [36]. This change is often accompanied by deletion or monosomy of chromosome 13.

The presence of t(4;14) correlates with aggressive course of MM. The IMWG and R-ISS defined t(4;14) as a HR CA [10, 37].

Translocation t(14;16)(q32;q23) and t(14;20)(q32:q12)

Translocation (14;16) is found in 2–5%, and t(14;20) in less than 2%, of patients with MM. These translocations are difficult to detect by conventional cytogenetics techniques [38], and lead to deregulation of *MAF* and *MAFB* genes. Increased MAF levels accelerate DNA division and synthesis in clonal plasmocytes [39]. In turn, overexpression of MAFB increases proliferation and drug resistance of clonal plasmocytes and is a high MM risk marker [40]. t(14;16) may be associated with lack of CD56 expression, contributing to high proliferative activity and worsening patient prognosis [41]. In patients with t(14;20), renal impairment is more common [42].

Translocation t(11;14) and t(6;14)

Translocation (11;14) is found in 15–20% of patients with MM and is the most frequently found translocation. Translocations t(11;14) and t(6;14) juxtapose the IgH enhancer with CCND1 (15–20%) and CCND3 (1–4%). Patients with t(11;14) show increased expression of cyclin D1 [43]. Patients with NDMM with isolated t(11;14) are classified as standard risk [4, 44]. Translocation (11;14) is more common in lymphoplasmacytic lymphoma, IgM monoclonal protein secretion, non-secreting MM, plasma cell leukemia, and AL amyloidosis.

Translocation (6;14) is found in a relatively small percentage (<2%) of all MM cases. High levels of cyclin D3 mRNA can be found in this abnormality [45]. When this translocation occurs, a dysregulation of the proto-oncogene MUM1, which can be identified by immunohistochemistry, is observed, providing a marker for identifying a positive conversion of BCL6 and its expression of CD138 [46, 47]. Patients with t(6;14) are also included in the standard-risk group [10].

Deletion of 1p/1q21 gain

1q21 gain is detected in 35–40% of patients with NDMM and in almost 68% of patients with RRMM, and is associated with a poor prognosis [30, 48–50]. It is represented by 1q chromosome duplication, unbalanced 1q arm translocation, isochromosomes, or step translocation. The frequency of chromosome 1q21 gain increases as MM progresses. Overexpression of the *CKS1B* gene, located in 1q21, is associated with drug resistance [51–53].

The deletion of 1p is less common than gain of 1q, but both share a poor prognosis. Most frequently deleted regions are 1p32 (CDKN2C), 1p22, and 1p12. The 1p deletion seems to worsen treatment outcomes [38, 54].

Deletion of 13q/monosomy of chromosome 13

Deletion of 13q occurs in approximately 45–50% of patients with MM, including monosomy 13 and interstitial deletions in up to 85% of cases [55, 56]. Patients with del(13q) are included in the HR group [10]. It often coexists with other HR CA, including t(4;14) [57]. Patients with a del(13q14) are more likely to have advanced disease, in addition to high serum levels of β_2-microglobulin, and a higher percentage of PCs in the BM.

Deletion 17/17p

One of the most important CA is deletion of 17p13, del(17p) [38, 58, 59]. It is observed in 5–12% of patients with NDMM and increases with disease progression, reaching 75% in relapsed/refractory (RR) MM [60–63]. TP53 deletion in MM is an HR factor and is associated with an unfavorable prognosis. This CA results in the loss of the *TP53* gene [64]. A mutation in the *TP53* gene occurs in c.50% of patients with del(17p). The presence of del(17p) is associated with an increased incidence of hypercalcemia, extramedullary forms of MM, including the central nervous system's involvement, and transformation into PCL. It seems that bi-allelic del(17p) worsens prognosis more than does the monoallelic [65]. The bi-allelic inactivation of *TP53* due to the presence of a mutation in one allele, and deletion in the other, is considered an ultra-HR factor.

Management of patients with cytogenetic high-risk MM

Proteasome inhibitor protocols (bortezomib, carfilzomib, ixazomib), IMiDs (thalidomide, lenalidomide, pomalidomide), dexamethasone, and anti-CD38 antibody (daratumumab [Dara]) are recommended for induction treatment patients with HR NDMM eligible for ASCT; however, not all of them are approved for use in the first line. Following complete remission (CR) treatment, >50% of patients had negative minimal residual disease [MRD(–)] [66–68].

The achievement of MRD(–) after daratumumab, bortezomib, thalidomide, dexamethasone (Dara-VTd) induction treatment has been shown to prolong PFS [55, 68]. The use of high doses of melphalan (HDMel) and ASCT remains the standard of care in young patients with MM, including HR MM [56]. Compared to carfilzomib, lenalidomide, dexamethasone (KRd) treatment (12 cycles), ASCT results in a higher rate of MRD(–) (90% vs. 72%) [66].

The EMN02 study showed that the use of tandem ASCT overcomes the unfavorable prognosis of cytogenetic risk (3-year PFS: 76% vs. 69%; p =0.48) [69]. This result was confirmed in the STaMINA study, which found benefit in PFS after tandem ASCT [70].

Lenalidomide maintenance treatment in patients with cytogenetic HR MM did not prolong PFS and OS compared to standard cytogenetic risk patients [71]. On the other hand, the use of bortezomib as maintenance therapy in HR patients is compelling. The use of bortezomib in induction and maintenance therapy improved the prognosis in this group of NDMM patients with CAs [65]. These results contributed to studies being conducted with other PIs such as carfilzomib and ixazomib. Carfilzomib was better than bortezomib, but it did not significantly improve the poor prognosis associated with del(17p) [72, 73].

Conversely, the use of ixazomib combined with lenalidomide and dexamethasone prolonged PFS in patients with del(17p) compared to the use of lenalidomide with dexamethasone (Rd) [74]. The use of ixazomib in maintenance therapy showed similar results in high- and standard-risk patients, with a median improvement in PFS of five months [75]. Promising results in patients with RRMM with del(17p) were obtained using pomalidomide combined with dexamethasone (Pd). The achieved PFS in patients with del(17p) was comparable to the standard-risk patients [76].

In the Forte trial, carfilzomib, lenalidomide, dexamethasone (KRd)-ASCT-KRd and 12 months KRd induced high quality responses, with good MRD(–) rates, and ASCT showed additional benefit in the HR population [66]. The use of novel drug-based chemotherapy protocols (VMP, VMP/VTP with VT maintenance or Rd)

Table IV. Treatments for patients with high cytogenetic risk multiple myeloma

NDMM — patients eligible for ASCT								
HR patients	VRd [84]	FORTE [66] KRd12 vs. KRd-T vs. KCd			CASSIOPEIA [55] Dara-VTd vs. VTd		GRIFFIN [67] Dara-VRd vs. VRd	
Post-consol CR rate [%]	34.8	49	51	–	37	33	NR	NR
NDMM — patients not eligible for ASCT								
HR patients	SWOG [85] VRd vs. Rd		ALCYONE [78] Dara-VMP vs. VMP		MAIA [79] Dara-Rd vs. Rd			
PFS, m	38	16	NR		NR		29.6	
HR (95% CI)	*p* =0.19		0.78 (0.43–1.43)		0.57 (0.32–1.04)			
Relapsed/refractory multiple myeloma								
HR patients	POLLUX [81] Dara-Rd vs. Rd		ASPIRE [73] KRd vs. Rd		CASTOR [86] Dara-Vd vs. Vd		OPTIMISMM [82] VPd vs. Vd	
ORR rate [%]	89	68	79.2	59.6	85	56	NR	NR
PFS, m	26.8	8.3	23.1	13.9	12.6	6.2	8.44	5.32
HR (95% CI)	0.37 (0.18–0.76)		0.7 (0.42–1.16)		0.41 (0.21–0.83)		0.56 (0.35–0.9)	

NDMM — newly diagnosed multiple myeloma; ASCT — autologous stem-cell transplantation; HR — high-risk; VRd — bortezomib, lenalidomide, dexamethasone; KRd12 — carfilzomib, lenalidomide, dexamethasone 12 cycles; KRd-T — carfilzomib, lenalidomide, dexamethasone, thalidomide; KCd — carfilzomib, cyclophosphamide, dexamethasone; Dara-VTd — daratumumab, bortezomib, thalidomide, dexamethasone; VTd — bortezomib, thalidomide, dexamethasone; Dara-VRd — daratumumab, bortezomib, lenalidomide, dexamethasone; post-consol — post consolidation; NR — [explanation?]; CR — complete response; Rd — carfilzomib, lenalidomide, dexamethasone; Dara-VMP — daratumumab, bortezomib, melphalan, prednisone; VMP — bortezomib, melphalan, prednisone; Dara-Rd — daratumumab, lenalidomide, dexamethasone; PFS — progression free survival; HR — hazard ratio; CI — confidence interval; Dara-Rd — daratumumab, lenalidomide dexamethasone; KRd — carfilzomib, lenalidomide, dexamethasone; Dara-Vd — daratumumab, bortezomib, dexamethasone; VPd — bortezomib, pomalidomide, dexamethasone; Vd — bortezomib, dexamethasone; ORR — overall response rate

in cytogenetic HR MM patients not eligible for ASCT improved the response rate compared to patients at standard cytogenetic risk, even though survival times remain much lower.

The IFM study showed that the application of the VRD protocol did not overcome the unfavorable prognosis in a group of elderly patients with MM with HR cytogenetics [77]. However, the use of daratumumab (Dara-VMP, Dara-Rd and Dara-KRd) improved PFS in patients with HR, although it was still shorter than in patients with standard cytogenetic risk [78–80]. In the treatment of cytogenetic HR MM recurrence in untreated or lenalidomide-sensitive patients, the longest PFS (26.8 months) was achieved with Dara-Rd (POLLUX) [81]. The combination of Rd with other drugs such as carfilzomib, ixazomib, and elotuzumab results in a shorter PFS, but the differences between patients with HR and SR are less significant than in the POLLUX study.

On the other hand, the use of the Pd protocol has a beneficial effect in patients with RRMM and del(17p) [76]. The use of other pomalidomide-based protocols (bortezomib–Pd and Isatuximab–Pd) has resulted in benefits in HR, and may overcome the unfavorable prognosis in HR cytogenetics [82, 83]. Table IV summarizes the treatments for patients with cytogenetic HR MM.

Conclusions

The introduction of genetic and molecular tests to MM diagnosis has resulted in a much better understanding of this disease's biology and has allowed a more accurate prognosis. Identifying HR CA has changed the staging system of MM and the method of treating patients with MM. Undoubtedly, further development of cytogenetic and molecular research should be expected in the coming years.

Author's contributions

GC, AJ, AS, DHV — wrote and critically revised manuscript.

Conflict of interest

None.

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None.

Ethics

The work described in this article has been carried out in accordance with The Code of Ethics of the World Medical Association (Declaration of Helsinki) for experiments involving humans; EU Directive 2010/63/EU for animal experiments; Uniform requirements for manuscripts submitted to biomedical journals.

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