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From ‘Me’ to ‘Us’: solidarity and biocitizenship in the Brazilian cancer precision medicine innovation system

De ‘Mim’ para ‘Nós’: solidariedade e biocidadania no sistema brasileiro de inovação em medicina de precisão para o câncer

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ABSTRACT As biotechnology innovations move from the bench to the bedside and, recently, also to the Internet, a myriad of emanating challenges and potentials may rise under distinct sociocultural and political economic contexts. Using a grounded-theory-inspired case study focused on the Brazilian research consortium for Medullary Endocrine Neoplasia type 2 (BrasMEN) – an inherited syndrome where genetic tests define cost-effective interventions – we outline facilitators and barriers to both development and implementation of a ‘public health genomics’ strategy under a developing country scenario. The study is based on participant observation at three centres and interviews with all who might hold an interest in MEN2 around Brazil. We discuss how a ‘solidarity’-based motivation for individual and collective ‘biocitizenship’ is driving people’s pre-emptive actions for accessing and making personalised healthcare available at Brazil’s Unified Health System (SUS) via the ‘co-production’ of science, technology and the culture for precision medicine – termed Brazil’s ‘hidden’ biomedical innovation system. Given the establishment of BrasMEN as ‘solidarity networks’ – promoting and supporting the cancer precision medicine’s rationale – our data illustrates how a series of new bioethical challenges raise from such engagement with familial cancer genomics under Brazil’s developing country scenario and how this social/soft technology constitute a solution for Euro/North American societies.

KEYWORDS Science, technology and society. Technological development and innovation projects. Multiple Endocrine Neoplasia Type 2. Solidarity. Brazil.

RESUMO Ao passo em que as inovações biotecnológicas migram da bancada para o leito e, mais recentemente, também para a Internet, uma miríade de desafios e potenciais pode surgir em contextos socioculturais e político-econômicos distintos. Usando um estudo de caso inspirado na teoria embasada em dados focado no consórcio de pesquisa brasileiro sobre a Neoplasia Endócrina Múltipla do Tipo 2 (BrasMEN) – uma síndrome rara em que testes genéticos definem intervenções custo-efetivas – ressaltamos facilitadores e barreiras para ambos desenvolvimento e implementação de uma estratégia de genômica em saúde pública no cenário de um país em desenvolvimento. O estudo foi baseado em observação participante em três centros e entrevistas com todos que podem ter um interesse sobre a MEN2 no Brasil. Discutimos como uma motivação baseada em ‘solidariedade’ para uma ‘biocidadania’ individual e coletiva está impulsionando ações preventivas nas pessoas para acessar e fazer com que

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cuidados em saúde personalizados sejam disponibilizados no Sistema Único de Saúde (SUS) do Brasil via a 'coprodução' de ciência, tecnologia e a cultura para medicina de precisão – denominado sistema de inovação biomédico brasileiro 'escondido'. Dado o estabelecimento do BrasMEN como 'redes de solidariedade' – promovendo e apoiando a abordagem da medicina de precisão em câncer – nossos dados ilustram como uma série de novos desafios bioéticos surgem desse engajamento com a genômica do câncer familiar no cenário de país em desenvolvimento brasileiro e como esta tecnologia social/leve constitui uma solução para sociedades europeias e norte-americanas.

PALAVRAS-CHAVE *Ciência, tecnologia e sociedade. Projetos de desenvolvimento tecnológico e inovação. Neoplasia Endócrina Múltipla Tipo 2. Solidariedade. Brasil.*

Introduction

As society creates and defies new scientific and ethical dilemmas in the post-genomic era¹, clinical diagnosis alone – symptoms, physical examination, biochemical and imaging tests – is not sufficient without the concomitant use of genetic tests to identify potentially affected individuals. Continuous research on genes and their signalling pathways inducing inherited diseases expands the understanding of human genetics, and offer unique opportunities for new approaches to prevention, diagnosis and treatment for various forms of illnesses such as cancer^{2,3}. In this sense, advances in precision medicine promote the development of novel biotechnologies to track altered genes and transform medicine's *modus operandi* around treatment, moving from symptomatic to a pre-symptomatic approach for patients' maximum benefit³.

These new 'technologies of the self'⁴ – i.e. genetic tests – carry novel challenges and dilemmas posed by a new culture of potentially enhanced health self-management. When physicians and researchers deal with patients and their families as they engage with genetic testing, for either preventive or curative purposes, in distinct sociocultural and political economic contexts in diverse

countries^{5,6}, bioethical issues arise under what has been termed as 'biological citizenship' ('biocitizenship') – to encompass all citizenship projects that have linked people's beliefs about the intersecting concepts of politics, identity and biology in the era of precision medicine³. This particular kind of 'biosocial identities' tend to gather health beliefs and perceptions about shared or collective health (genetic) risks and responsibilities within an ethics of (self) care and empowerment^{7,8}. The limits to 'biocitizenship' have already been outlined at Euro/North American contexts, and according to this evidence, 'biocitizenship' and patient 'empowerment'

consists of a more complex cluster of relationships between the molecular and the population. The biological existence of different human beings is politicised through different complementary and competing discourses around medical therapies, choices at the beginning and end of life, public health, environment, migration and border controls, implying a multiple rather than a singular politics of life⁹⁽⁷¹¹⁾.

In this sense, there is the need to consider socio-ethical, cultural and political economic facilitators and barriers for both the development and implementation of a precision

medicine approach in countries outside Euro/North American contexts. Comprehension of national and local circumstances and demands are necessary to help understand different types of societal motivations for individual and collective citizenship driving pre-emptive actions for accessing and making precision medicine available. For this, we developed a grounded theory-inspired case study that included participant observation in São Paulo, Ceará and Espírito Santo regional centres of the Brazilian Multiple Endocrine Neoplasia Type 2 (MEN2) research consortium (BrasMEN) and conducted first-person interviews with all who hold an interest in a national precision medicine rationale for MEN2 across Brazil, i.e. patients, family members, health professionals, researchers, policy and decision-makers. We focused on MEN2 as it constitutes a rare example of research in precision medicine where genetic testing enables disease risk-classification defining cost-effective clinical interventions for timely personalised curative and/or preventive treatment^{10,11}. We aimed to observe how, where and who engages with cancer precision medicine for public health purposes in a developing country like Brazil.

The BrasMEN case study

MEN2 is a syndrome including MTC, pheochromocytoma, primary hyperparathyroidism, and other abnormalities and follows an autosomal dominant inheritance¹⁰ – meaning that, if the carrier inherits the mutated gene from only one parent, he or she has a greater chance of developing the disease. The study of its biology has had unique implications for the establishment of comprehensive and integrated clinical services comprising genetic testing to manage patients and their families affected by this rare disease.

Over 95% of MEN2 patients carry different single-nucleotide mutations in the gene RET (REarranged during Transfection). These mutations promote constitutive activation of the tyrosine-kinase transmembrane receptor in thyroid

C-cells, which promotes tumorigenesis¹⁰. For this reason, depending on the mutation found, a positive genetic test for germline RET mutations – that can be transmitted onto one or all progeny – can determine people's risk for manifesting the disease. According to the tiered-risk classification – from 'A', low, to 'D', high – health professionals' shared decision-making with patients and families drives clinical interventions, ranging from asymptomatic thyroidectomy to metastatic follow-up and tyrosine-kinase receptor inhibitor trial therapeutics^{10,11}.

For asymptomatic high-risk RET-mutation carriers, prophylactic thyroid removal implies lifelong referral for daily hormonal reposition. For symptomatic patients carrying high-risk RET-mutations and MTC, thyroidectomy referral may also include cervical central and/or bilateral lymph nodes dissection, adrenalectomy for pheochromocytoma, as well as selective resection of parathyroid glands for primary hyperparathyroidism, and regular follow-up to verify post-surgical absence of MEN2 signs and symptoms over a five years period. Otherwise, low- to moderate-risk RET-mutations carriers may share decision-making with health professionals based on regular (six months) image and biochemical investigation for nodule and/or tumour growth, hormonal changes (elevated calcitonin and metanephrines) and other MEN2 symptoms that characterise disease outbreak and/or progression, all of which may engender surgical referrals^{10,11}.

A recent study investigating depression, anxiety, quality of life and coping in long-standing MEN2 patients in Brazil¹² deployed its semi-qualitative approach to pair patients psychological and clinical status. Here, our work aims to bridge this gap in robust qualitative – grounded theory-based – methodologies to not only identify but contextualise such consequences of both MEN2 individual and familial genetic testing in Brazil. Hence, given the recent national politicisation of rare genetic conditions – with both public health system (Unified Health System – in Portuguese, Sistema Único de Saúde, SUS) and private

health insurance plans now obligated to pay for genetic testing for some rare diseases, including breast cancer and MEN2^{13,14}, besides the wider context of judicialisation of health – especially in terms of accessing new high cost drugs and interventions¹⁵, our BrasMEN case study provides a unique and timely scenario to underline socio-ethical, cultural and political economic barriers and facilitators to the efficient and effective implementation of a cancer precision medicine approach outside Euro/North American contexts.

Methodology

Participants and recruitment

Following ethical approval (Federal University of São Paulo REC 0468/10), after a first interview with health professionals at BrasMEN founding centre in São Paulo (n=9), snowball sampling was deployed and an invitation to conduct interviews was two-fold: health professionals and decision-makers were sent e-mail messages with participant information and informed consent forms; patients and family members were approached individually during remote centre's clinical assistance visits, when participant information, informed consent and interviews occurred. Health professionals and decision-makers were interviewed according to respondents' availability. Interviewees comprised three sample groups: 16 patients-participants, 21 health professionals and 4 decision-makers (summarised in *chart 1*).

Inclusion criteria were: health professionals (n=14) and (clinical) researchers (n=6) involved with MEN2 in Brazil; patients (n=8) and relatives (n=7) at all levels of clinical assistance (pre- and post-genetic testing-counselling / thyroidectomy / follow-up) within the BrasMEN consortium; user (n=1) and provider (n=1; health professional) of direct-to-consumer genetic testing in Brazil; and representatives (n=4) of

governmental agencies involved with regulation of genetic tests nationally. Exclusion criteria were failure to: agree with informed consent, response to invitation contact after two trials, and validate narrative after interview. Response to invitation was 78.85% (41/52) and 100% for narrative validation.

Data collection

Participant observation notes^{16,17} derived from fieldwork during clinical consultations at three BrasMEN centres where patients-participants were interviewed: São Paulo, Ceará and Espírito Santo. Information on other interviewees are summarised in *chart 1*. All forty-one interviews lasted between one and two hours and were audio-recorded, transcribed and 'transcreated' into oral life history narratives¹⁸. All interviews were conducted as a series of in-depth semi-structured open-ended questions meant to introduce interviewees to talk about individual/familial/professional experience with the subject, and from which further questions derived. Exploratory questions focused on: individual/familial/professional experience with MEN2 and/or RET genetic testing and/or precision medicine; perceptions about the future of precision medicine; perceptions and attitudes about sociocultural, ethical, political, economic, and regulatory facilitators and barriers for the implementation of ongoing genetic testing programs in Brazil; individual future plans.

Data analysis

We based our methods on grounded theory, as both development and implementation of diagnostic molecular genetic testing for cancer and its regulation are complex and require conceptually dense theory emanating from empirical data. This methodological approach can account for a great deal of variation in the studied phenomena¹⁹. All data was coded, according to arising and/or previously outlined themes drawing from fieldwork notes and

systematic analysis of interview narratives. Codes were summarised with respective quotations in spreadsheets for manual analysis. Quotes are representative, illustrating selected

themes that met saturation criteria. Anonymity was guaranteed for all interviewees. Narratives underwent respondent validation for internal validity of collected data²⁰.

Chart 1. Summary of participants' descriptors

| ID | Gender | Age (Years) | Professional Activity | Social/ Econ Status | Study Role/ Status |
|----|--------|-------------|---------------------------|------------------------|---|
| P1 | Female | 15-20 | Student | Low | SP patient: RET mutation carrier; MEN2 metastatic |
| P2 | Male | 45-50 | Bricklayer | Low | SP patient: RET mutation carrier; MEN2 metastatic |
| P3 | Female | 20-25 | Hairdresser | Low | SP patient: RET mutation carrier; MEN2 metastatic |
| F1 | Male | 40-45 | Accountant | Average | SP family member: negative RET; no MEN2 |
| F2 | Female | 40-45 | Surgery Assistant | Average | SP family member: negative RET; no MEN2 |
| F3 | Female | 50-55 | Entrepreneur | Average | SP family member: negative RET; no MEN2 |
| C1 | Female | 30-35 | Endocrinologist; Academic | High | BrasMEN founding centre clinical researcher |
| C2 | Male | 30-35 | Endocrinologist | High | BrasMEN founding centre clinical researcher |
| C3 | Male | 35-40 | Endocrinologist; Academic | High | BrasMEN founding centre clinical researcher |
| S1 | Male | 45-50 | Surgeon; Academic | High | BrasMEN founding centre head surgeon |
| S2 | Male | 35-40 | Surgeon; Academic | High | BrasMEN founding centre surgeon |
| T1 | Female | 55-60 | Biomedical Researcher | High | BrasMEN founding centre RET sequencing technician |
| T2 | Female | 55-60 | Biomedical Researcher | High | BrasMEN founding centre RET sequencing technician |
| C4 | Male | 60-65 | Endocrinologist; Academic | Highest | BrasMEN founding centre diagnostic tests clinical researcher |
| R1 | Female | 45-50 | Biologist; Academic | High | BrasMEN founding centre precision medicine researcher |
| P4 | Female | 30-35 | Cosmetologist | Low | CE patient: RET mutation carrier; initial MEN2 symptoms |
| P5 | Female | 50-55 | School Teacher | Low | CE patient: RET mutation carrier; BOC/MEN2 metastatic |
| P6 | Male | 25-30 | Agronomist; Politician | Average | CE patient: RET mutation carrier; initial MEN2 symptoms |
| F4 | Female | 40-45 | Nurse | Low | CE family member: RET mutation carrier; no MEN2 symptoms |
| F5 | Male | 60-65 | Historian; Academic | Average | CE family member: unscreened |
| C5 | Female | 30-35 | Endocrinologist; Academic | High | CE BrasMEN remote centre clinical researcher |
| S3 | Male | 35-40 | Surgeon; Academic | High | CE BrasMEN remote centre head-neck surgeon |
| P7 | Female | 30-35 | Lawyer | High | ES patient: RET mutation carrier; MEN2 metastatic |
| P8 | Female | 60-65 | School Cook/ Cleaner | Low | ES patient: RET mutation carrier; MEN2 thyroidectomy referral |
| F6 | Female | 55-60 | Administrator | Average | ES family member: RET mutation carrier; MEN2 thyroidectomy |
| F7 | Female | 60-65 | Pathologist; Academic | Highest | ES family member: negative RET; no MEN2 |
| C6 | Female | 40-45 | Endocrinologist | High | ES BrasMEN remote centre clinician |
| R2 | Female | 40-45 | Biologist; Academic | Average | ES BrasMEN remote centre translational medicine researcher |
| C7 | Female | 50-55 | Endocrinologist; Academic | High | SP remote centre clinical researcher |
| R3 | Male | 25-30 | Medicine Student | High | SP remote centre translational medicine researcher |
| C8 | Female | 40-45 | Endocrinologist; Academic | Highest | SP reference centre clinical researcher |
| S4 | Male | 55-60 | Surgeon; Academic | High | SP reference centre head-neck surgeon |

Chart 1. (cont.)

| | | | | | |
|----------|--------|-------|-------------------------------|---------|---|
| C9 | Female | 45-50 | Endocrinologist | High | RJ BrasMEN remote centre clinician |
| C10 | Female | 35-40 | Endocrinologist; Academic | High | MG BrasMEN remote centre clinical researcher |
| C11 | Female | 50-55 | Endocrinologist; Academic | High | RS reference centre clinical researcher |
| C12 | Female | 40-45 | Endocrinologist; Academic | High | SP private sector clinical researcher |
| 23andMe | Male | 60-65 | Investment Banker | Highest | SP 23andMe user; no RET mutation carrier; no MEN2 |
| Anvisa | Male | 40-45 | Biologist; Decision-Maker | High | FD national market registration decision-maker |
| ANS | Female | 40-45 | Paediatrician; Policy-Maker | High | RJ national private health insurance plans decision-maker |
| SBPC/ ML | Male | 40-45 | Pathologist; Policy-Maker | High | RJ national association diagnostic medicine president |
| Conitec | Female | 60-65 | Infectologist; Decision-Maker | High | FD Ministry of Health HTA Agency director/ decision-maker |

23andMe (US-based privately held personal genomics and biotechnology company) Anvisa (National Health Surveillance Agency); ANS (National Regulatory Agency for Private Health Insurance and Plans); SBPC/ML (Brazilian Society of Clinical Pathology/Laboratory Medicine); Conitec (National Commission for the Incorporation of Technologies into SUS, Health Technology Assessment Agency of the Ministry of Health of Brazil); SP (São Paulo State); CE (Ceará State); ES (Espírito Santo State); RJ (Rio de Janeiro State); MG (Minas Gerais State); RS (Rio Grande do Sul State); FD (Federal District; Brasília); BOC (Breast and Ovary Cancer).

Results

Brazil's 'hidden' biomedical innovation system: 'co-production' of science, technology and the cancer precision medicine culture via solidarity networks

A - THE SOUTHEAST-SOUTH AXIS OF EXPERTISE AND TECHNOLOGY CONCENTRATION

During fieldwork, we observed that BrasMEN comprises seventeen national research and clinical assistance groups from six federative states (Ceará, Espírito Santo, Minas Gerais, Rio de Janeiro, Rio Grande do Sul and São Paulo) with large expertise in cost-effective MEN2 clinical management with RET-mutations testing and associated symptoms description for a large number of patients (n=2,201) and families (n=176)¹¹. São Paulo is the founding reference centre of BrasMEN, thus focusing on more complex and aggressive MEN2 cases referred from all over Brazil, and on prophylaxis for children carrying mutations. The Espírito Santo cohort was first identified in São Paulo – proband patient referral to access

the BrasMEN precision medicine's *modus operandi* revealed a new RET mutation¹¹. Ten years after first local assistance to screen and follow-up one large (seven generations) MEN2 family (n=728), we encountered people at all ages and stages of health care regarding existing: RET-mutation identification, MEN2 symptoms manifestation, curative or preventive surgery and follow-up. The majority presented high mean level of education and higher than average socioeconomic status, mainly relying on private insurance plans for long-term healthcare access. First local assistance in Ceará identified and assisted (potential) MEN2 carrier individuals (n=113). Families lived in a rural area, presented high levels of consanguinity (several first-cousin marriages) and lower than average socioeconomic status, generally relying on the public health system (SUS) to access health care.

On the BrasMEN cancer precision medicine's *modus operandi*, an experienced surgeon explained that by replicating international MEN2 guidelines¹⁰ in Brazil, they “managed to live, today, part of what the future holds for medicine in this area [...] [as] many serum biomarkers will be replaced by genetic tests”.

Corroborating previous literature findings on the European MEN2 research consortium

– EuroMEN²¹ – all health professionals (n=21) outlined the relevance of BrasMEN for the establishment of a national MEN2 precision medicine's *modus operandi*. Despite its cost-effectiveness, the perception of all interviewees is that, today, access to genetic testing remains scarce, mainly restricted to the southeast-south axis of expertise and technology concentration in Brazil. Most patients-participants (n=11/16) and all health professionals (n=21) and decision-makers (n=4) illuminated on how such regional disparities reflect the way health care and technology have been unequally developed and distributed around Brazil, historically^{22,23}, especially in the case of clinical genetics services^{24,25}. This finding corroborates previous conclusions from a World Health Organization (WHO)²⁶ consultation on community genetics services for genetic disorders in developing countries.

During fieldwork, narratives from patients-participants and health professionals alike confirmed our participant observations on this barrier, as both expertise and tools to implement MEN2 precision medicine approach remained restricted to three reference centres: two in São Paulo and one in Rio Grande do Sul. Widening the availability and access to genetic testing and follow-up care in the north, north-east and centre-west regions was observed as key to all respondents.

All BrasMEN health professionals (n=21) and most patients-participants (n=9/16) viewed both SUS and Brazil's biomedical innovation system – the 'health industry complex'^{22,24,27} – as non-developed and with scarce resources. According to national *in vitro* medical devices entrepreneurs, innovation must meet local demand to grant people access²⁸ and produce an impact on national public health priorities²⁹.

B - BRAZIL'S 'HIDDEN' BIOMEDICAL INNOVATION SYSTEM

Recognising such regional disparities as a barrier for the implementation of precision

medicine as a public health initiative in a developing country scenario, BrasMEN researchers developed an arrangement that we termed Brazil's 'hidden' biomedical innovation system. This terminology refers to how cancer genetic testing has been developed in UK's hospitals and research institutions – under what has been named 'hidden research system'³⁰.

Differently from the UK's 'hidden research system', the BrasMEN arrangement additionally aims to rectify the aforementioned unequal access to such comprehensive and integrated clinical service encompassing clinical genetics for patients who would otherwise remain unidentified and/or unassisted²⁴. During fieldwork, we observed how health professionals deployed funding from state-sponsored research grants for the establishment of this 'hidden' biomedical innovation system for RET-mutations testing and follow-up centralised in São Paulo – this constitutes the basis for the Brazilian 'health industry complex'.

According to all health professionals (n=21) and several patients-participants (n=8/15) this 'friendly arrangement' constitutes BrasMEN's underlying 'tiers-1 and 2 solidarity' ethos, and a facilitator for the implementation of precision medicine into SUS, under a developing country scenario. These respondents described BrasMEN as the 'co-production'³¹ of science (new RET mutations and associated MEN2 symptoms epidemiological data description), technology (cost-effective RET mutations identification) and a new culture for prevention in health³.

On the other hand, several health professionals (n=10/21) were concerned that over-relying on BrasMEN may undermine policy and decision-makers' recognition of the real demand for a cancer precision medicine approach to adequately manage MEN2 patients and families across Brazil. During fieldwork, we observed that the majority of BrasMEN patients/participants (four patients, three relatives) and all health professionals deployed individual out-of-pocket investments to ensure delivery of the BrasMEN's *modus operandi*.

Therefore, BrasMEN case study illustrates these 'hidden' initiatives for the construction of 'need' (i.e. demand) for clinical usership³² of genetic screening for both diagnosis and follow-up of a large group of MEN2 patients in the Brazilian public national health system as a public health strategy for accessing value chains through this new market-building of the *in vitro* diagnostic medical devices sub-sector of the Brazilian 'health industry complex'. In this sense, 'tier-3 level of solidarity enactment' as contractual and legal manifestations would constitute a key political economic and regulatory facilitator to the efficient and effective implementation of a cancer precision medicine approach outside Euro/North American contexts. Now, we outline how BrasMEN 'solidarity networks' enacted both tiers-1 and 2 of a 'solidarity'-based ('global south' type of) 'biocitizenship'.

C - 'TIERS-1 AND 2 SOLIDARITY NETWORKS'

Deepening ourselves into participants' self-reported motivation for engaging with the BrasMEN's *modus operandi*, the majority of patients-participants (n=12/15) based it on two areas of reasoning. First, participation enabled molecular diagnosis for the family; hence, granting access to adequate therapeutics in a timely manner for all mutation-carriers. Corroborating previous MEN2 literature data¹², patients-participants viewed themselves as gatekeepers to access alongside health professionals.

Second, there was a willingness to contribute to scientific scholarship so that other potentially affected families around Brazil might also benefit from the research consortium's outcomes – the solidarity-based ethos. Their reasons were narrativised in relation to feeling 'safe', 'confident', 'grateful' and in terms of the 'need to reciprocate'.

Health professionals' additional motivation for participating was that they also recognised being affected in at least one relevant aspect with fellow health professionals and/

or patients-participants. They further commented feeling 'happiness', 'satisfaction for contributing', 'professional achievement' and 'mission' as they narrated individual and professional motivations for participating at BrasMEN.

Moreover, all stakeholders' (n=35) self-reported motivations for participating at the BrasMEN arrangement referred to both 'tier-1 personal level of solidarity enactment' and 'tier-2 group practices'², commenting that their common goal was assisting each other secure MEN2 patients' and families' sustained wellbeing. All health professionals (n=21) and most patients-participants from Ceará (n=5/5), Espírito Santo (n=3/4) and São Paulo (n=3/6) argued that their willingness to assist others was not only based on family ties (shared biological/ DNA making or 'blood'). They recognised others as 'fellows in the same journey' as they experienced ignorance, despair, resignation and hopelessness in the face of future suffering upon themselves and the life of others whom they assisted – regardless whether 'others' were health professionals, patients or family members. This two-fold identification – individuals under: similar biological features (genetic mutations and/or disease manifestation); and/or similar affections (suffering, privation and inequity) – drove not only the 'personal level of solidarity' enactment (tier-1 solidarity), but also the 'group practices' (tier-2) we observed. Moved by 'common goals', such stakeholders manifested 'willingness to carry costs to assist others [who [we]re all linked by means of a shared situation or cause] with whom [they] recognise[d] sameness or similarity in at least one relevant respect'², via the 'trust, safety and reciprocity' networks they created within BrasMEN. These 'solidarity networks' constitute the basis for the 'me' to 'us' shift in respondents' attitudes around BrasMEN's *modus operandi*.

Our data shows how this 'solidarity'-based 'biocitizenship' constituted a facilitator for the implementation of a Brazilian type of 'global

south' solution for a 'public health genomics' initiative that enabled a more sustainable and equitable opportunity for cancer precision medicine outside Euro/North American contexts. Still, do our findings illustrate other facilitators and barriers for the implementation of the stakeholders' claims for (tier-3 solidarity via) contractual and other legal manifestations for the incorporation of an ongoing RET-screening program within SUS for MEN2?

New bioethical challenges in cancer precision medicine under 'solidarity networks' in Brazil

We now outline how a series of new bioethical challenges we observed during fieldwork are being differently managed within BrasMEN, as compared to findings from Euro/North American contexts. Our data also illuminates which bioethical challenge constituted a facilitator or a barrier to the implementation of a 'public health genomics' initiative as a 'global south' social³³/soft technology^{34,35} (i.e. processes of human interaction, in the sense of thinking scientific methods/*modus operandi* to deal with social structures, human relationships and motivation techniques) that is both more sustainable and equitable under Brazil's developing country scenario.

A - FEARS, UNCERTAINTY, DENIAL, STIGMATISATION AND DISCRIMINATION

Similar to Euro/North American MEN2 studies¹⁰, BrasMEN patients-participants presented no difficulty in communicating: 'fears' and 'uncertainty', especially regarding lack of continuity of care, 'relief' for negative test results, and 'reliance' on family and health providers for information and support. Different from Euro/North American findings, BrasMEN health professionals enumerated 'religious reasons', 'fatalism', and 'denial' as the most common reasons for refusal to undergo genetic testing and/or surgery. Such attitude

mainly occurred for patients from lower socio-cultural and/or socioeconomic strata outside the southeast-south axis in Brazil.

Counterbalancing those barriers, according to health professionals (n=6/21) who pursued part of their careers in Euro/North American countries, sociocultural differences constituted a facilitator for the implementation of BrasMEN's *modus operandi* as health professionals engaged 'more openly' with patients.

According to a clinical researcher, the 'trust, safety and reciprocity' networks created under BrasMEN 'tiers-1 and 2 solidarity'-based 'biocitizenship' constituted another facilitator for the implementation of its precision medicine's *modus operandi*. Letting families with different RET-mutations and distinct levels of MEN2 manifestation spontaneously exchange their individual/familial diagnostic and disease experiences during clinical visits constituted one of the key aspects of BrasMEN social/soft technology – a 'global south' solution to fears, uncertainty, denial, stigmatisation and discrimination.

Regionally, we identified two barriers for the implementation of such *modus operandi*. First, we observed fears about stigmatisation and/or discrimination for patients-participants from higher sociocultural and/or socioeconomic strata, especially those carrying low-risk RET-mutations under longer (ten years) follow-up (São Paulo n=4/6; Espírito Santo n=3/4) along the southeast-south axis. Health professionals (n=9/21) further illustrated how unidentified and/or undiagnosed family members from such cohorts seemed more reticent about undergoing testing and/or (curative/prophylactic) treatment, depending on different individual and/or familial: disease understanding, risk perception (for disease outbreak and progression) and stigmatisation/discrimination.

Second, during fieldwork, we observed concerns about environmental interferences on disease outbreak and progression at the Ceará cohort (n=5), as people learned about the increasing cancer prevalence after plane-pulverised harvests were established locally by multinational enterprises³⁶. Therefore,

patients-participants from higher sociocultural and/or socioeconomic strata carrying better prognosis (lower-risk gene mutations) might have constituted a barrier due to fears of stigmatisation/discrimination, despite BrasMEN 'solidarity'-based 'biocitizenship' enactment that has otherwise prevented it for patients-participants from lower sociocultural and/or socioeconomic strata. Looking deeper into this profile during fieldwork, as we searched for reasons for such barrier, we observed various levels of 'lay expertise'.

B - 'LAY EXPERTISE' AND 'GENETICISATION'

Although the majority of patients-participants interviewed (n=13/15) fully understood the genetic compound about the disease, health professionals reported difficulty when approaching families from lower sociocultural and/or socioeconomic strata about BrasMEN's prophylactic and early detection goals, especially at remote regions (n=4/20). All BrasMEN endocrinologists (n=12) revealed that 'lay expertise' about such new culture for prevention enhanced patient adherence, thus constituting a facilitator to the implementation of BrasMEN's *modus operandi*.

We further observed how the engagement with genetic testing and/or the BrasMEN's *modus operandi* changed individual and/or familial perception about various aspects of the disease's symptoms and diagnosis. Most BrasMEN patients-participants (n=12/16) from all regions pre-emptively searched for health information on the Internet and/or with relatives or friends with previous professional experience in the health sector. In this sense, 'lay expertise' constituted a facilitator within BrasMEN.

Outside BrasMEN, the direct-to-consumer genetic test user explained how 'lay expertise', in fact, constituted a barrier to the implementation of precision medicine worldwide by arguing that knowledge translation on both molecular biology and clinical genetics, including probability concepts, must improve to aid 'early adopters' of such new health

technologies fully understand their genetic reports – this includes not only patients and/or consumers but also health professionals and society in general. All decision-makers (n=4) and health professionals (n=21) agreed with this argument, mentioning the need to formalise what types of health professionals can deliver genetic counselling, and the adequate types of training they must undergo before talking with patients and/or consumers.

'Geneticisation' also constituted a barrier outside BrasMEN. Despite two surgeons' positive attitude towards wider availability of genetic testing, three BrasMEN (clinical) researchers, the private health sector (direct-to-consumer) genetic test developer and all decision-makers commented similar concerns, further suggesting the potentiality for over-prescription and over-diagnosis. Their negative perceptions followed counselling Brazilians who bought direct-to-consumer genetic tests on the Internet, as they worried about 'geneticisation'³⁷ and the lack of a comprehensive regulatory context guiding genetic testing and all clinical activities that could engender stigmatisation, discrimination and over-prescription of non-directed clinical interventions.

The Anvisa (National Health Surveillance Agency) decision-maker also commented that the current regulatory context does not forbid the direct-to-consumer availability of genetic testing but, at the same time, requires a medical referral/prescription to enable the access to any type of health technology. He also discussed how both national regulatory and political-economic environment do not seem inclined to change in the near future (2022). Therefore, differently from previous MEN2 findings in Euro/North American societies, the BrasMEN 'tiers-1 and 2 solidarity'-based 'biocitizenship' prevented 'lay expertise' and 'geneticisation' from becoming barriers to a 'global south solution' for the implementation of a 'public health genomics' initiative under the Brazilian developing country scenario due to how individual and familial genetic

counselling was delivered by the consortium's *modus operandi*.

C - 'BOUNDARY WORK' AND JUDICIALISATION OF MEDICINE

Deepening ourselves into the underlying reasons of how BrasMEN 'tiers-1 and 2 solidarity'-based 'biocitizenship' enabled this successful genetic counselling delivery, we observed the relationship between patients-participants and BrasMEN health professionals. Although the majority of patients-participants interviewed (n=13/15) fully understood their participation in a research initiative, the private sector (ANS – National Regulatory Agency for Private Health Insurance and Plans) decision-maker remained sceptical about patients' full comprehension of the thin 'boundary' over what was deemed research and clinical assistance in the BrasMEN's *modus operandi*.

Health professionals (n=3/21), decision-makers (n=4) and the three patients-participants who underwent private health insurance discrimination commented on the 1988 Constitution 'solidarity' and 'humanitarian right to health' ethos²³. Two key aspects based their concerns: first, the recent politicisation of rare genetic conditions in Brazil, with SUS now paying for genetic testing for some rare diseases^{13,25,38}. Second, the post-1988 Constitution wider context of judicialisation of health, with the growing demand by those who remain unattended by SUS and cannot afford private health insurance plans, fuelling a consumerist approach to health care and technologies. During fieldwork, participant observation data confirmed such health consumerism findings – especially for the increasing out-of-pocket consumption of genetic testing, as outlined by both direct-to-consumer genetic testing user and the private sector genetic test developer. These fieldwork findings also refuted the 'therapeutic misconception' hypothesis³⁹, as most health professionals and patients-participants, in fact, presented a positive attitude towards such 'lack of boundary' over what

was deemed research and clinical assistance. Therefore, both 'lack of boundaries' and the judicialisation of medicine have so far constituted facilitators for a public health genomics initiative as part of BrasMEN's *modus operandi*.

D - 'BIOPOWER' AND 'BIOCITIZENSHIP'

Given all findings thus far support the tier-3 solidarity claims made by stakeholders, first we outline that most BrasMEN patients-participants (n=13/15) illuminated how 'lay expertise' played only a partial role in individual, familial and shared decision-making among patients/families and health professionals. Therefore, indicating that the BrasMEN's *modus operandi* helped surpass 'lay expertise', 'geneticisation', 'boundary work' and 'judicialisation' barriers.

Second, more experienced health professionals (n=6) and two decision-makers (ANS and SBPC/ML – Brazilian Society of Clinical Pathology/Laboratory Medicine) commented on the controversial issue of autonomy versus paternalism²⁵. However, few BrasMEN patients-participants (n=6/15) – from those (n=13/15) who recognised such 'boundary work' – actively negotiated their '[bio]power to define, describe and classify normality as well as abnormality'. These respondents presented higher than mean level of education, previous experience in the health sector (i.e. professional or familial/individual disease experience) and lived along the southeast-south axis in Brazil.

Unlike other more prevalent cancer types such as breast and ovary cancer syndrome, or other rare genetic disorders, we did not identify any patients' associations or advocacy groups for MEN2 in Brazil, thus far, as opposed to the UK, confirming our findings. This constitutes both tiers-1 and 2 of solidarity enactment² that we observed, as all patients-participants (n=15) and health professionals (n=21) regarded both health professionals' and patients-participants' commitment, availability, openness and knowledgeable attitude as 'ideal', while absent outside BrasMEN. This is

why the 'tiers-1 and 2 solidarity'-based 'biocitizenship' BrasMEN enabled, in fact, surpassing most potential barriers we identified for the implementation of this cancer precision medicine tool in Brazil – at both public and private sectors. In this sense, our findings illuminate how the stakeholders' claims for the incorporation of the RET-mutation test (with adequate individual and familial genetic counselling, as established by the BrasMEN's *modus operandi*) into SUS constitutes the 'tier-3 solidarity'-based 'biocitizenship' via contractual and other legal manifestations for a Brazilian 'public health genomics' initiative, more sustainable and equitable than other precision medicine implementation alternatives at Euro/North American contexts⁴⁰.

Discussion

Precision medicine is the means through which governments are distancing themselves from their citizens⁴¹, by sharing the biomedical collective's chief task with lay people – enhancing their responsibility to self-regulate their health status. These empowered 'biocitizens' shape new ways of understanding, judging and acting on themselves, as well as on those to whom they owe responsibilities. These groups may encompass offspring, family members, health professionals, co-citizens, and ultimately, their community and society. Consequently, via such forms of 'biological collectivisation', these moral pioneers, 'as prudent yet enterprising individuals', engage in new practices of biological choices within a 'regime of the self'. Their demands include recognition of lay expertise, access to biotechnologies, and financial support from governmental authorities to act upon themselves, via social activism^{3,4,7}.

Different from this type of 'biocitizenship' – defined as such due to the context where it has arisen (i.e. USA^{7,8}) – and the more generally described paternalism exerted by health professionals in Brazil – as outlined by a group of clinical geneticist/researchers from southern

Brazil²⁵ – our findings outline a 'solidarity'-based 'biocitizenship': our first novelty. We argue that Brazil's underlying socio-ethical, cultural and political economic contexts, as observed both on fieldwork notes and oral life history narratives, influenced the way through which people have been engaging with cancer precision medicine tools and enabling their co-production for a 'public health genomics' culture around Brazil's developing country scenario.

Ashton-Prolla et al.²⁵ outlined how "molecular genetic testing was accessible only through a few commercial laboratories, for patients able to pay out-of-pocket, or through research projects in reference centres". Our case study findings further illuminate how both the research consortium and the 1988 Constitution 'solidarity' ethos comprised the socio-cultural and political-economic basis for promoting this different type of individual and collective citizenship, based on what we termed the 'trust, safety and reciprocity' networks – BrasMEN 'solidarity networks'. In this sense, our findings outline how all stakeholders developed a 'global south' solution to not only help each other but also compensate for the historical, sociocultural and political economic processes around how health care and innovations have been differently developed and distributed sub-nationally – chiefly associated with state-funded academic reference research centres along the southeast-south axis^{22-25,42-45}. This is our second innovative finding: BrasMEN 'solidarity networks' as basis for the national 'health industry complex' for cancer/rare diseases.

All BrasMEN stakeholders deployed the concept of 'solidarity' to describe how each part, "as singular and essentially autonomous actors, form[ed] social and political coalitions out of their free will [...] by bonds of mutual assistance and common goals"² to enable the BrasMEN's 'hidden' biomedical innovation system for the co-production of such high-risk health technologies – i.e. molecular genetic diagnosis/prognosis. This is what differentiates BrasMEN's *modus operandi* from the

UK's 'hidden research system': 'tiers-1 and 2 solidarity'-based 'biocitizenship'. This type of 'biocitizenship' is

framed less as an individuated rights-based discourse and more in terms of perception of risk and danger that reflect common, shared and collective accountability for health and illness⁴⁶.

For this reason, we argue that our findings evidence the enactment of 'tier-1 (personal level) solidarity' from the 3-tiered bioethical conceptualisation of 'solidarity'², whereby tier-1

includes both [individual] enactments of willingness to assist others which would incur relatively small costs [...] and those which would incur significant costs².

We further argue that, if 'tier-1 solidarity' had not occurred, there would be no guarantee that contractual and legal manifestations (tier 3) would have enforced real group practices (tier 2) as institutionalised conduct to both develop and implement genetic testing around Brazil, as previously discussed by Osada²⁴ and observed in this case study. In fact, it was the tier-1 solidarity enactment that enabled the spontaneous appearance of group practices (tier-2), fostering the stakeholders' claims for the incorporation of RET-screening into SUS, under contractual and legal manifestations (tier-3) by the health technology assessment agency of the Ministry of Health of Brazil – Conitec (National Commission for the Incorporation of Technologies into SUS).

We also observed similarities of restricted availability and access to a cancer precision medicine rationale with other non-developed scarce-resources national health systems regarding local primary healthcare programs, as previously discussed for a catholic nuns-led breast and ovary cancer syndrome BRCA1/BRCA2 genetic testing and follow-up monitoring health service for women at risk/or

manifesting breast and ovary cancer in Cuba⁴⁷. Our BrasMEN findings presented further similarities with the more religious-based sociocultural practices grounding people's philanthropic behaviour around pastoral care (and paternalism) as reported for Greek Orthodox Christians, when compared to other Euro/North American societies for this same cancer type⁴⁸. Therefore, we questioned the existence of a potential 'global south' (tiers-1 and 2) 'solidarity'-based 'biocitizenship' – our third innovative finding. As foreseen by Rabinow and Rose⁸, if this pre-symptomatic interventions model is to be deployed as a national public health program,

not only in the developed but also in the less developed world, the logics of medicine and the shape of the biopolitical field [will] be altered, and new contestations [will] emerge over access to such technologies and the resources necessary to follow their implications.

Our findings favour such predictions for the Brazilian developing country scenario.

It could be argued that our findings confirm and illustrate Ashton-Prolla and colleagues'²⁵ point that the Brazilian population holds potentiality to fully portray the 'biological citizenship' as described for Euro/North American societies due to the rising consumerism of precision medicine tools. Our findings support that most health professionals and decision-makers – besides the direct-to-consumer genetic testing user – have already reproduced and/or encountered the more consumerist attitude towards healthcare for health technologies users, at both private and public health sectors, due to fashion, persuasive marketing, or 'hypochondria', especially along Brazil's southeast-south axis¹¹ – our fourth innovative finding. Before the 1988 health system reform, private healthcare insurance plans proliferated around Brazil, fuelling a consumerist approach to health care and technologies uptake, which only deepened inequity causing a consequent crisis in the social security system and reform

aspiration²³. Given SUS's and Brazil's 'health industry complex' non-advanced and scarce resources context, millions are still denied access to basic health technologies and care being used for over half a century. Hence, the consequent construction of the 'need'/demand (consumerism) for the clinical usership of cancer precision medicine that the BrasMEN 'solidarity' case study tries to avoid by proposing a more sustainable and equitable 'global south' solution via a public health genomics initiative. The aim is to avoid judicialisation of medicine.

Within the wider context of the 'humanitarian right to health' in Brazil, the issue of accessing new (and/or old) high cost health technologies – drugs and interventions⁴⁹ – called both private (ANS) and public health (Conitec, Anvisa, SBPC/ML) sectors decision-makers' attention about new opportunities for public health policy-making to change national and subnational rationale for accessing and establishing clinical genetics services. Our findings, however, do not overly favour Rabinow and Rose's prediction for the development of the more neoliberal precision medicine's trend for enhanced health self-management outside a 'medicalised' environment in Brazil. Given BrasMEN 'tiers-1 and 2 solidarity'-based 'biocitizenship', our data revealed that the sociocultural context about how health, disease and death are perceived – as patients and families are more 'emotionally demanding' at the personal level towards health professionals – differs from those from Euro/North American MEN2 findings¹⁰⁻¹² – our fifth innovative finding. Our data further illuminates the way BrasMEN 'solidarity networks' constituted the driving-force for this shift from 'me' to 'us' in stakeholders' attitude around how, where and who accesses and adheres to precision medicine, at both public and private sectors. These findings corroborate previous literature findings on cancer genomics implementation in Brazil²⁴. More importantly, our findings support that BrasMEN 'solidarity networks' have helped solve some of the new bioethical challenges

that Euro/North American societies have been facing. By discussing the barriers and facilitators we observed under the BrasMEN case study, we can offer Euro/North American countries a 'global south' solution for those developing and implementing cancer precision medicine as a more sustainable and equitable public health strategy.

Differently from Euro/North American societies, when facing fears, uncertainty, denial, stigma and discrimination, BrasMEN patients-participants did not rely exclusively on 'genetic test results' – i.e. 'lay expertise' and 'geneticisation' – in a 'political economy of hope'⁵⁰, through which the biotechnologies of today will disclose cures and/or treatments for the future. Instead, patients-participants also relied on family, health professionals and, ultimately, on the BrasMEN 'solidarity networks' for information and support – the 'global south' solution. In this sense, we reiterate the limits of 'biosociality' to genetic testing because

geneticisation resonates with a number of themes that are seen as characteristic of neoliberal government, in which risk, choice and individual agency and responsibility are central organising ideas⁵⁰⁽²⁹¹⁾.

We did not observe this more neoliberal type of 'biosociality' within the BrasMEN case study – our sixth innovative finding.

BrasMEN 'friendly agreement' was paramount to help MEN2 patients, RET-mutations carriers, and health professionals support each other emotionally, financially and with the adequate level of health information and technologies as people started feeling safer, and trusted family members and health professionals. 'Tiers-1 and 2 of solidarity'-based 'biosociality' helped BrasMEN stakeholders manage risk, choice, agency and responsibility collectively, once the cancer precision medicine as a public health strategy was established locally. In this sense, we observed no boundary over stakeholders' agency as people helped each other communicate and

translate what they ‘know’ about cancer, genes, screening and familial diseases from an experiential perspective.

The BrasMEN health professionals’ willingness to share their biomedical collective responsibility for managing an individual’s health status with patients and families – the successful genetic counselling *modus operandi* – was a facilitator for individual/familial engagement and adherence to the cancer precision medicine as a ‘global south’ solution for a public health genomics initiative – our seventh innovative finding. Therefore, bridging this governmental gap in investments and sustainable public policies for the establishment of a precision medicine approach to tackle cancer as a public health issue, genetic testing and counselling engendered patients-participants’ and health professionals’ ‘biopower’ negotiation to construct family pedigrees. Our BrasMEN case study offers providential evidence for the fallibility of genetic tests (or better of ‘geneticisation’). Their potentiality for false-negatives and/or false-positive results can promote not only further uncertainty in patients and families, but also distrust, which attempts against professional and institutional integrity, besides requiring better ‘articulation’ skills from all parties involved in prophylactic approaches of healthcare delivery⁵¹. Under such scenario, our findings illustrate how all collectively articulated their respective expertise to translate the individual lexicon employed by each party involved, when going from one social world to the other, without losing their inherited meaning through verbal communication. It is at tiers-1 (personal) and 2 (group practices) of the intersecting social worlds – where technologies go from the bench to the bedside, and vice versa – that we observed how BrasMEN ‘global south’ solution is innovating the 21st century of precision medicine and big data analysis as a successful ‘public health genomics’ initiative.

Finally, on the judicialisation issue, the three cases of private health insurance discrimination and stigmatisation identified along

Brazil’s southeast-south axis reverberated the health professionals’ and decision-makers’ worries about wide implementation of genetic testing without prior discussion about an adequate regulatory context to guarantee systematic confidentiality of genomic individual (and big) data, as well as adequate training for health professionals performing genetic counselling. Given the high-rate consumerism along Brazil’s southeast-south axis and the rising marketing perspectives for non-directed genetic testing, our data suggests the pursuit of the stakeholders’ regulatory claims.

Concluding remarks

Despite having a public health system that is scarce in resources under Brazil’s developing country scenario, the BrasMEN initiative developed a ‘global south’ solution to invest in risky developments such as a cancer precision medicine to tackle a public health issue in a more sustainable and equitable manner than has been established in Euro/North American contexts for MEN2.

Our case study illuminates how the BrasMEN ‘solidarity networks’ can be proposed as a developing country (‘global south’) solution to mend such a risky investment and a series of bioethical challenges that have been identified as barriers to both development and implementation of precision medicine in Euro/North American countries – where they also rely on a ‘hidden research system’ for cancer genetic diagnosis. In this sense, we propose that the BrasMEN experience can become a pilot for testing a ‘public health genomics’ initiative as a way of reaching spaces outside the scope of the southeast-south axis in Brazil.

Most importantly, we reiterate that our work is the first to bridge this gap in robust qualitative – grounded theory-based – methodology and offer in depth findings on both psychological and social consequences of committing to undergo MEN2 prophylactic and/or curative treatment based on genetic testing,

globally. We also outline that our findings are generalisable within the scope of familial cancer precision medicine and/or rare diseases, for which access to high-cost and high-density technologies such as genetic testing constitutes a matter of both social (amongst patients, family members and governments) and professional (amongst clinicians, clinical and/or genetics/molecular biology researchers) dispute. In this sense, our case study illuminates how Brazilian health professionals are actively sharing their biomedical collective's chief task with lay people – enhancing a collective responsibility onto self-regulating individual and familial health status – as means to overcome paternalism and its health system's shortcomings via a new form (a 'global south' type) of 'biocitizenship': the 'solidarity'-based 'biocitizenship' – a Brazilian new (social/soft) technology in health.

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Collaborators

Authors contributed differently to the development of this manuscript: Sousa MSA (0000-0001-5806-3790)* contributed substantially with: 1) the conception, planning, analysis and interpretation of data, 2) the drafting and critical revision of the content, and 3) the participation in the approval of the final version of the manuscript. Gallian DMC (0000-0002-5452-215X)* contributed with: 1) the conception and planning of data analysis, and 2) critical revision of the content; and Maciel RMB (0000-0002-6123-6098)* contributed substantially with: 1) the planning and interpretation of data, 2) critical revision of the content, and 3) the participation in the approval of the final version of the manuscript. ■

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