The CAPCI network: A CAncer Prostate Consortium of India for conducting next-generation genomic sequencing studies

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ABSTRACT

The CAncer Prostate Consortium of India (CAPCI) was established in September 2020 by a group of researchers and clinicians interested in identifying inherited and somatic risk factors that are related to the onset of prostate cancer (PCa). The consortium aims to improve the patient care and treatment in India by exploring and expanding the utility of genomic repositories associated with PCa. These aims are achieved by advancing discovery in genome science particular to Indian phenotypes, translating scientific discoveries into improved standards of care. One of the vital goals of the consortium is to combine the data from the western, European and other ancestries, and identify common and exclusive risk profiles associated with PCa in Indian scenarios. These findings would additionally allow us to validate them in experimental settings to explore the molecular mechanisms underlying pathogenesis of PCa besides understanding new personalized therapeutic regimens.

KEYWORDS: Genomics, Consortium, Prostate cancer, Genetic variants, Collaborative convergence.

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Introduction

The CAncer Prostate Consortium of India (CAPCI) network is a Bioclues.org and Brainpan.co supported consortium of six institutions. The network was formed to explore the utility of genomic repositories associated with prostate cancer (PCa) for advancing discovery in genome science particular to Indian phenotypes, further translating scientific discoveries to improved standards of care. We strive to carry out this mission by ensuring efficient sample collection, research and development besides educating the stakeholders to address the issues related to social stigma associated with PCa.

Organization

The institutional sites, *viz*. Amrita School of Biotechnology, Amrita University, Kollam, Birla Institute of Scientific Research (BISR), Jaipur, Rukmani Birla Hospitals (RBH), Jaipur, Mahatma Gandhi University of Medical Sciences and Technology (MGUMST), Jaipur, University of Rajasthan (UoR), Jaipur, Indian Institute of Chemical Technology (IICT), Hyderabad, Sawai Man Singh (SMS) Hospital, Jaipur and Queensland University of Technology (QUT), Brisbane, Australia form academic partners while DNA Xperts, Noida., Theracues, Bengaluru and Tissuegnostics, Austria form industrial partners, supported by the scientists of these network groups in the areas of genomics, next generation sequencing, clinical research, big data and machine learning. Bioclues.org serves as a hub for bringing together the steering committee composed of principal investigators responsible for accomplishing goals for the development of these scientific panels. The consortium page can be found at www.bioclues.org/capci.

Current progress and future activities

The consortium efforts began in early 2020 with seed funding obtained from Brainpan.co in 2018. As the collaborators converged, there was a need to bring equivocal thoughts, action and debate on the emerging areas of PCa research. The consortium sub-network got their first publication in 2020 in PCa genomics from their pilot analysis of sequencing (Gupta et al., 2020). From the first few meetings that were setup, the network peers discussed the need for bringing India specific phenotypes for which samples would steadfastly be used for sequencing, genotyping that are largely focused in the areas of indolent tumors, benign prostatic hyperplasia (BPH), malignant and radical prostatectomy. We agreed to come up and emerge as a consortium of cross-network initiatives through a community consultation. We further discussed expanding the network of all regions and states in India by maintaining the diversity of PCa phenotypes (Figure1). Currently, over 30 scientists and clinicians are a part of this cohesive group as we convene four times a year.

Over the last few years, diminutive knowledge about the etiology of PCa has largely been known. The patient risk group is clearly articulated largely for elderly men, albeit consequently majority of therapies and aetiological disquisitions have centered on male sex hormones (Patel & Klein, 2009). After an initial positive response to these treatments, PCa eventually progresses to a more resistant and androgen independent form, which is usually untreatable and lethal within 2 years of recurrence on average. India has largely seen a steep increase in incidence of PCa and palliative care during the past two decades (Vlachostergios et al., 2017). The population based cancer registry for 2020 shows ca. 48,000 casualties and as many

as a million cases pan-India (Global Cancer Observatory, n.d.).. Given the paradigm shifts in incidence and casualties, multi-centric collaborative efforts are required to bring about a change in patient detection, treatment, and care, and this is where we believe the CAPCI add values.

Indian context of human genome project

The human genome project (HGP) is one of the significant projects in biological sciences and clinical medicine with a major impact on clinical medicine in understanding the molecular and biochemical interactions of every individual (Emmert-Streib et al., 2017). In particular, it has given us an impetus to understand the diversity as reflected by the various polymorphisms occurring in genes of our genome. The chance of acquiring a polymorphism is one in 1000/base pairs in the genome, single nucleotide polymorphisms (SNPs) being the most common. On an average, 4 to 8 SNPs can be located in any gene whether it is in the exonic region or in the exon-intron boundary. These SNPs are now used to target and track the gene of interest through whole genome studies. This has led us to understand how altered gene expression and its altered regulation play a role in disease manifestation. Such a molecular level of understanding makes it possible for us in present times to design potential therapies for different ailments and their classifications (Lele, 2003). Hence, after the HGP, for the first time ever, there are a whole lot of repositories on genetic variation of diseases, pan-cancer genomes etc. and all the diseases. While this has led to growth in computational biology, managing huge amounts of genomic data across the world has set a big data challenge (Gibbs, 2020). On the other hand, it has brought changes in Indian research from the last decade, as growth of the biotechnology industry for designing personalized medicine is more intended (Nogrady, 2018). India harbors not only cultural diversity but also genetic diversity as a result of a heterogeneous population. The Indian population structure is basically reflected by set marriage patterns and consanguinity practices.. As a result, the burden of rare or even extremely rare disorders is increasing in India. Genomics based approaches are capable of speeding up the diagnosis and management of such rare conditions. For such technologies, the Genomics for Understanding Rare Diseases: India Alliance Network (GUaRDIAN) consortium was formed to provide genomics solutions in India (Sivasubbu and Scaria, 2019). In 2020 Department of Biotechnology (DBT) has launched a project 'Genome India Project' (GIP) for creating Indian reference genome. Such an initiative shows India's growth in gene therapies and is a step towards raising next generation medicine (Bajaj. 2020). Under an 'IndiGen' program, whole genome studies were carried out and publicly available population databases called 'IndiGenomes' were created which are not only at the population level but also at the individual level. This database has already helped both researchers and clinicians identify causal genetic factors for any condition. As an all-inclusive resource for a total of about 18 million genetic variants of Indian population specifically, It includes single allelic genetic variants from genomes of geographically distinct populations, allele frequency, allele count, allele number, number of heterozygous and homozygous were also calculated (Jain et al., 2021). However, given this paucity of data on PCa, there are no reported variants specific to Indian

phenotype until we explored through our pilot study. Given the number of sporadic and hereditary PCa cases that might be associated, we therefore believe CAPCI could bring a pivotal change in exploring these understudied avenues.

International consortia on PCa

The National Institute of Health (NIH) funded post-GWAS initiatives with the establishment of ELucidating Loci Involved in Prostate Cancer SuscEptibility (ELLIPSE) (dbGaP, https://www.ncbi.nlm.nih.gov/projects/gap/cgi-bin/study.cgi?study_id=phs001081.v1.p1). As part of this, the Clinical ELLIPSE Consortium (CEC) was formed to develop risk models, analyze risk profiles and investigate clinical applications. Other consortia include the Prostate Cancer Association Group to Investigate Cancer Associated ALterations in the genome (PRACTICAL) which is a section of the Collaborative Oncological Gene-environment Study (COGS) along with other three cancer genetics consortium of breast, ovarian and BRCA1/2 mutation carriers (Szulkin et al., 2015). To provide specific prevention and screening approaches for those men who are at higher risk, SNPs were shown more promising to use for genetic risk profiling (Martens et al., 2016).The consortia efforts resulted in making the prostate-specific antigen (PSA) testing as not the only essential or sensitive test regimen avoiding the apparent conflicting results from two of the largest screening trials, the European Randomized Study of Screening for Prostate Cancer (ERSPC) and Prostate, Lung, Colorectal, and Ovarian (PLCO) cancer screening trial have elicited a strong debate among the experts. The National Cancer Institute (NCI) Mouse Models of Human Cancers Consortium (MMHCC) has also assembled a group of pathologists from both human and veterinary departments to inspect and discuss the present animal models for their recommendations in pathological analysis (Ittmann et al., 2013). On the other hand, the International Consortium of Prostate Cancer Genetics (ICPCG) brought together the genome wide linkage data taken from 11 different international prostate cancer research (PRCA) groups (Camp et al., 2007; Schaid & Chang, 2005). The Prostate Cancer Consortium in Europe (PEACE) assisted Europeans in gaining faster access to the most recent treatment options and data generation in the fight against PCa (Fizazi et al., 2015). Chinese Prostate Cancer consortium-Risk Calculator (CPCC-RC) (Chen et al., 2014), was designed in 2016 based on Gleason grade cancer (7 or above) in Chinese or other Asian countries who are exposed to the same genetic and environmental background. Furthermore, to address the PCa burden in black men, a consortium named "The Prostate Cancer Transatlantic Consortium (CaPTC)" was formed in 2005 (https://epi.grants.cancer.gov/captc/). This is an open consortium, which has a group of PCa scientists, clinicians, legal personnel and survivors from all across Europe, North America, the Caribbean Islands, and West Africa. The main aim of CaPTC is to explore differences in morbidity and mortality among black men and further study reliable biomarkers in addition to developing sensitive diagnostics approaches to remove the global disparity associated with PCa in black men (Oladoyinbo et al., 2020).

CAPCI organization, goals and objectives

The main goal of CAPCI is to promote collaboration between clinicians and academic researchers which will also help in knowledge exchange between these two groups. The CAPCI is

dedicated to developing programs that will lead to better approaches for prevention, diagnosis, and management of cancer, besides contributing to the broader agenda of PCa control in the country (Figure1). Although early linkage analyses and candidate gene approaches are used to identify variants, this coordination would be of great importance when we discuss adequate sample sizes, investigate the genetic–clinical interactions. Even though authentic statistics of associated risk and combined relationship of these SNPs could be established on a large-scale case-control evaluation, as previously described (Kote-Jarai et al., 2008), these cases have important implications for public health as well as individualized PCa management strategies. Having said this, broader scientific collaborations are needed for better organization of data quality and to protect confidentiality of participants as well. India has seen varied phenotypes of diabetes as a lifestyle disease. It is surprising that though India receives splendid sunshine and is one of the largest milk producers, the vitamin D deficiency is immense and what is more concerning is that these are susceptible to urogenital cancers/PCa. Furthermore, the diet based mutations associated with pCa risk from our pilot study (Gupta et al. 2020) further augments the hypothesis that there are a growing number of genetic contributions not just associated with disparities but also from epigenetics, environment and socio-economic status which motivates us to assess the objectives based on the varied phenotypes.

1. To establish PCa as a public health priority and a leading healthcare disparity in the Indian context.
2. To aid in research and development, education, data storage, curation, and public awareness in the direction of saving lives and improving patient outcomes
3. To collect data for inherent storage, entry and downstream data curation

Patient longitudinal follow-ups

The most important things to consider for disease classification studies are a proper sample size and statistical evaluation. Any influence of age on the study population and specific demographics should be taken into account. Use of archival samples can be challenging because of potential DNA/RNA damage (Gaffney et al, 2018; Jackson et al., 2012). Regular check-ups of subjects in the case of longitudinal cohort studies may increase a candidate's health when information is fed back to them. Screening for PCa for those with normal PSA (<4ng/ml) must be done in conjunction with (a) annual digital rectal examination (DRE) beginning at the age of 50 (b) PSA screening with 4k (kallikrein tests) and discussed with a health care provider as a yearly test amidst ages of 55-69. (c) procuring a positive family history, screening intended to be divulged amongst a healthcare benefactor, starting at age 40 (Catalona and Loeb, 2010). If PSA/DRE results are alarming, they can be supported by prostate ultrasound and biopsy (Schroder et al, 2001). Active surveillance (AS) of notably low risk PCa is recommended, in which PSA is screened every 6 months, DRE performed every 12 months, and repeat biopsy approximately every 12 months (Nieboer et al, 2018). On the other hand, approximately 30% of men are found to have higher grade PCa at repeat biopsy. Post recovery from PCa is also statutory as multifarious therapy has side effects such as hormone therapy (castration therapy) resulting in low testosterone, hot flashes, osteoporosis, loss of muscle mass, weight gain, erectile dysfunction,

decrease mental sharpness, depression, fatigue and increased cholesterol levels. Monitoring PSA and DRE after definitive therapy is compulsory, if the risk of recurrence is high (Loeb et al. 2007). The DRE could be performed early, regardless of whether the PSA is undetectable as patients treated with radiation therapy have a truncated, but measurable PSA. Prevalence of some psychological morbidity (distress, anxiety and depression) is also reported in PCa patients who can both directly or indirectly influence the patient's outcomes (quality of life). Earlier mental status in these patients was given less attention; however nowadays it has been critically included as a part of high quality cancer care during longitudinal follow ups (Kershaw et al., 2008) (Punnen et al., 2013).

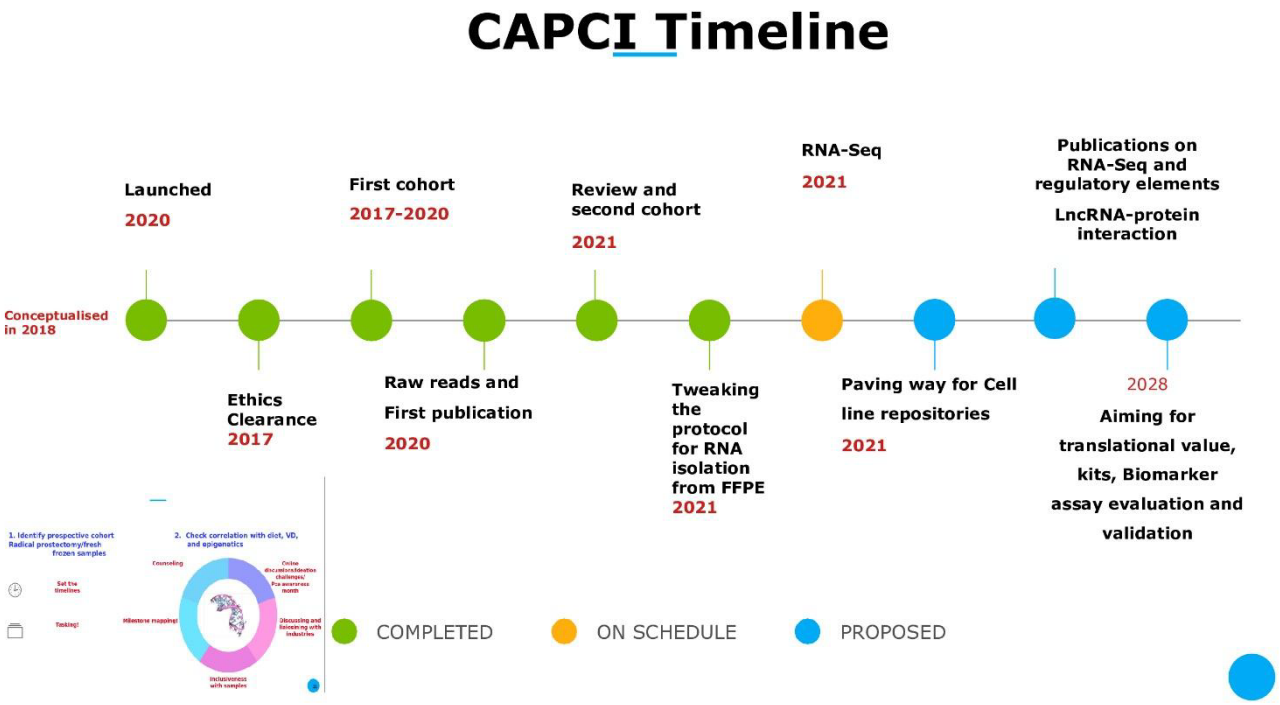

Figure 1: A pictorial representation of CAPCI inception, current developments and future goals

Overcoming sample conundrum for isolation of biomolecules for next generation sequencing

Over the years, several genome wide association studies (GWAS) have yielded substantial PCa risk alleles/SNPs in various populations. By and large, the African American (AA) population is largely affected followed by European American (EA) when compared to other sub-population across the world. However, a very limited number of next-generation sequencing (NGS) strategies have been done to ascertain the risk of PCa. We at CAPCI foresee that it is inevitable to sequence as many samples to identify risk alleles associated with the genetic contribution of PCa. This is also due to the supporting evidence that the GWAS has probably not identified the SNPs associated with PCa risk, accounting for the lack of PSA in the

African population which leads us to study this in developing countries including India. The NGS would allow us to identify a number of variants in tumor samples in a clinical setting. Whole Genome Sequencing (WGS) or Whole Exome Sequencing (WES) could serve as a diagnostic determinant in identifying new mutations. This is ably supported and followed by Sanger sequencing which validates the analyzed regions to accomplish sufficient depth of coverage or to create data of superior quality and further checks for downstream validation (Li et al., 2020).

In addition, the CAPCI aims to establish a new collaborative site for the collection of tissues for research that would be essential for PCa screening. From our prior experience in handling the samples, we hope to document sustainable goals for isolation should be performed. In biomedical research, to ensure effortless identification of specimens, correct labeling and barcoding of each specimen of tissue is paramount. Unlabeled and/or mislabeled (e.g., illegible handwriting) specimens might present a great clinical risk, which can be prevented by using a proper and defined method of labeling. Holistically, barcodes can be an efficient way of labeling. Developing and implementing a barcode system will allow links to construct high-throughput analysis of tissue microarrays (TMAs). TMAs are basically tissue "archives" developed by the recurring transfer of small tissue cores, from paraffin embedded 'donor' blocks into a single TMA 'recipient' block. The TMAs represent a unique approach of simultaneous analysis of up to 1000 different tissue samples at the DNA, RNA or protein level by immunohistochemistry (IHC), in situ hybridization (ISH), or immunofluorescence (IF). TMAs could be obtained from tissue repositories which provide a section of TMAs to investigators and preserve precious raw material (archived tissue samples). We have recently tweaked a protocol for the extraction of biomolecules from formalin-fixed, paraffin embedded (FFPE) tissue blocks that would be used for downstream sequencing analysis (Shukla et al. 2021)

Cell lines in PCa research

Cancer cell lines are developed as a significant model system for research based studies into the molecular mechanisms underlying the various aspects of PCa. *In vitro* studies with cancer cell lines can be used to identify novel gene candidates and investigate different molecular mechanisms. PCa resulting from different cell sources in the prostate lead to the development of a large number of PCa cell lines. PCa cell lines can be of two types i.e. androgen independent and androgen dependent. A database of the great number of PCa cell lines has been provided by British Columbia Cancer Agency (BCCA) and another detailed and comprehensive compendium of PCa cell lines is available from Sobel and Sadar (Russell & Kingsley, 2003).

The availability of different prostate cancer cell lines that mimic human disease progression is a challenging task. Prostate cell lines developed from patients have been instrumental in advancing research in understanding mechanistic details of cancer progression. There are two types of PCa, hormone-sensitive and hormone-resistant. Hormone-sensitive PCa responds well to androgen deprivation therapy (ADT), but most patients relapse with aggressive hormone-resistant PCa after an initial therapeutic response. The mechanism of hormone resistance isn't well understood and therefore appropriate prostate cell line models would assist in delineation of associated pathways. The most common prostate

cell lines include (i) non-cancerous prostate epithelial cell lines including RWPE-1, BPH-1, pRNS-1-1, RC77N/E, HprEpC etc; (ii) Hormone sensitive prostate cancer cell lines including LNCaP, LAPC-4, LAPC-9, VCaP, MDA-PCa 2a/2b, LuCaP 23.1, RC-77T/E etc; (iii) Hormone resistant prostate cancer cell lines including PC-3, DU-145, C4-2/C4-2B, 22Rv1, ARCaP etc (Saranyutanon et al., 2020). The major disadvantage of existing cell lines is that they are either derived from normal tissue or malignant tissue and are established by gene transduction using human telomerase reverse transcriptase (hTERT) (Murofushi et., 2006). Therefore, apart from using established cell lines, an effort will be made to establish patient-derived PCa cell lines of epithelial and mesenchymal origin. The acquisition of these cell lines would enable a thorough study of the mechanisms underlying hormone resistance in prostate cancer (Namekawa et al., 2019).

The culture of human cell lines requires appropriate biosafety Labs (BSL). Bio safety cabinet is a set of biocontainment facilities to grow and propagate biological agents. The cell lines that do not contain human or animal pathogens are designated BSL-1. BSL-1 is selected for agents that present minimal potential hazard to personnel and the environment. However, primary cell lines, cell lines transformed by human oncogenic viruses, fresh or frozen tissue explants are required to be handled using BSL-2 facility. BSL-2 is designated for all the agents associated with human diseases that pose a moderate health hazard. The National Centre for Cell Sciences (NCCS), Pune has been at the center of providing such cell lines for multifarious fields of cell biology, conspicuously those addressing imperative human health affairs such as cancer, integrating modern and conventional disciplines including cell biology, cellular signaling, stem cell biology, immunology, genomics, proteomics and systems biology. (National Centre for Cell Science, n.d.)

Need for PCa biobank

A biobank is a biorepository that stores human biological samples and provides access for scientific research. While research on these samples is non-therapeutic, it is not directly applicable to the donor/patient. Classification is based on either (a) specific disease or condition along with possible control data collection specifically designed for non-therapeutic research or existing collections with samples that were used for diagnosis, or (b) population or cohort studies wherein phenotypic (lifestyle/medical/ environmental) data associated with genetic data, would be used as a resource for different types of research. The convenience in the latter is that it provides a better understanding of the prevalence of gene variations and relation between phenotype and genotypes. Participating in research may pose a limited physical and emotional risk... Confidentiality may be an issue due to concerns that third parties (insurers, employers, schools, and the government) may gain access to data, the risk of personal or group stigma, and the sensitivity of medical and genetic data. A stigmatization for 'fair institutions' and societal access, privacy protection could be done by security, anonymization or coding of identifiable samples which would also be beneficial for biological materials that are traceable.

Informed consent could include allowing people to assess the risk for themselves, honoring their participation, and stressing the divide between research and medical care. Many patients or donors are reluctant in some complex consent procedures. Nevertheless, it could be useful if

disease/condition is treatable and volunteers have a right to this kind of information. To overcome this, commercial companies should share a part of the profit with people who need it the most (benefit sharing). For example, collections of blood spot cards could be used to study prevalence of cancer susceptibility genes. Research progress should be communicated with the participants in a detailed and transparent manner either via personal interaction or website/newsletter. There should be a policy for providing information related to preventable diseases and those details need to be included in informed consent forms. It would have the right to entreat citizens to partake in akin research. On the other hand, PCa biobanks could allure the general public to scrub in genetic research on the kernel of solidarity provided the aim of such research is to aid diagnosis and treatment of PCa conditions. We aim to develop this as an extended program with industry partners wherein a biobank containing biospecimens, coupled with both clinico-pathological and epidemiological data would be used for collaboration of urologists, scientists, pathologists and research personnel. Blood, urine and prostate tissue could be obtained, systematically processed in a timely fashion and banked on site using standard operating procedures. Although a few biobanks in India such as sapinebio have off-shoot, there needs to be strict informed consents and anonymised patient specimens with affiliated clinical data implemented

Road ahead

The CAPCI is aimed to bridge the gap between cancer geneticists and clinicians/urologists associated with PCa diagnosis. Screening genomic parameters for PCa will discover functional aspects which in turn will help in understanding pathogenesis and chemo preventive therapeutic measures. As we strive for ample statistical data that could be helpful in explaining genetic-clinical and genetic-epidemiological data, a reliable risk predicting model could ease the screening and treatment regimen (Goh et al., 2012). On the other hand, standard operating procedures (SOPs) are not properly framed and with very limited progress in this field in India, efforts to distinguish between indolent and aggressive tumors could be on the anvil. This can be possible largely due to reproducibility of data pertaining to tumor heterogeneity observed in the same patient between primary and metastatic lesions. One can address the heterogeneity problems through Spatial Transcriptomics approach, especially using TMA/FFPE sections (Brady et al., Nature communication, 2021).The CAPCI's establishment of SOPs would aid in developing a better method of data evaluation obtained from different centers with focus on sample collection and storage along with improving DNA, RNA and protein extraction methodologies. A need for establishment of biobanks to achieve a decent amount of source material for future studies would provide an impetus and this is only possible by bringing collaborative convergence to the fore, as we say "ome" (many ~ together).

Declarations

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Authors' contributions

PS ideated and conceptualized framework for CAPCI. SS and BDK wrote the first draft with DS,

NS and PS. Other authors chipped in with lateral sections.

Availability

http://www.bioclues.org/capci

Competing Interests

The industrial partners as a part of this consortium including the academic authors do not have any conflicts of interests. Bioclues.org is a not-for-profit organization which propounded the CAPCI.

Ethics Approval

Not applicable

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None

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