Using CCTA to diagnose CAD improves patient outcomes

By Kate Madden Yee, AuntMinnie.com staff writer

January 17, 2023 -- Coronary CT angiography (CCTA) improves coronary artery disease (CAD) outcomes by reducing hospitalizations for heart attacks and mortality rates, a study published January 11 in *JACC: Cardiovascular Imaging* reported.

ELSEVIER

JACC: Cardiovascular Imaging

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In Press, Corrected Proof

Original Research

National Trends in Coronary Artery Disease Imaging: Associations With Health Care Outcomes and Costs

Jonathan R. Weir-McCall PhD [a, b], Michelle C. Williams PhD [c], Anoop S.V. Shah PhD [d], Giles Roditi MBChB [e], James H.F. Rudd PhD [a], David E. Newby PhD [c], Edward D. Nicol MD [f, g]

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Methods

Investigations from 2012 to 2018 were extracted from a national database and linked-hospital admission and mortality registries. Growth rates were adjusted for population size, with image modality use, cardiovascular hospital admissions, and mortality compared using Kendall's rank correlation. The impact of CG95 was assessed using an interrupted time-series analysis.

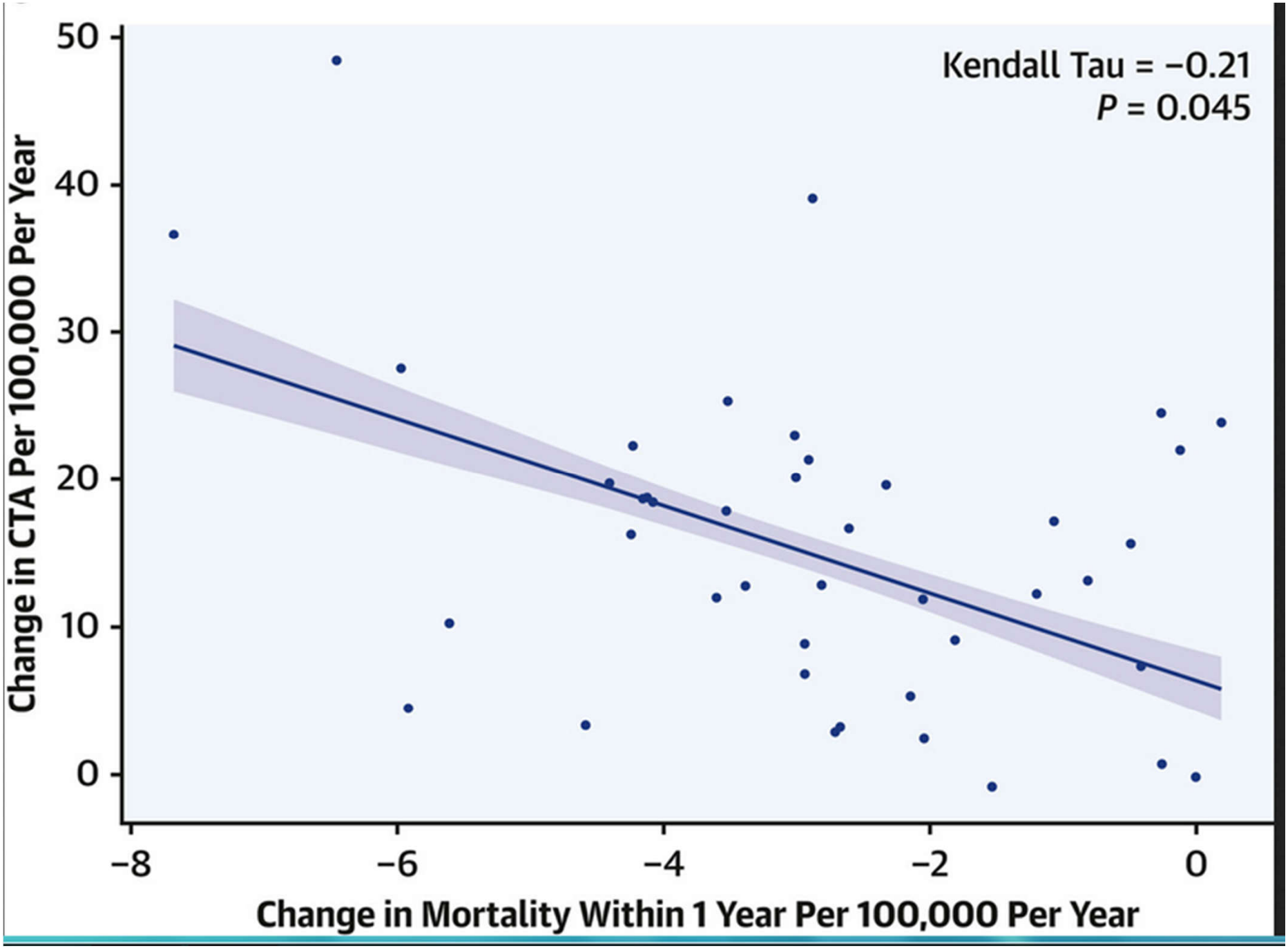
Results

A total of 1,909,314 investigations for CAD were performed, with an annualized per capita growth of 4.8%. Costs were £0.35 million/100,000 population/year with an increase of 2.8%/year mirroring inflation (2.5%/year). CG95 was associated with a rise in CCTA (exp[β]: 1.10; 95% CI: 1.03-1.18), no change in myocardial perfusion imaging, and a potential modest fall (exp[β]: 0.997; 95% CI: 0.993-1.00]) in invasive coronary angiography. There was an apparent trend between computed tomography angiography growth and invasive catheter angiography reduction across regions (Kendall Tau: −0.19; $P = 0.08$). CCTA growth was associated with a reduction in cardiovascular mortality (Kendall Tau: −0.21; $P = 0.045$), and ischemic heart disease deaths (Kendall Tau: −0.22; $P = 0.042$), with an apparent trend with reduced all-cause mortality (Kendall Tau: −0.19; $P = 0.07$).

Conclusions

Imaging investigations for CAD are increasing. Greater regional increases in CCTA were associated with fewer hospitalizations for myocardial infarction and a more rapid decline in CAD mortality.

Central Illustration


Kendall Tau = −0.21
P = 0.045
Change in CTA Per 100,000 Per Year
50
40
30
20
10
0
−8
−6
−4
−2
0
Change in Mortality Within 1 Year Per 100,000 Per Year

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Original Article

Hepatitis B virus pre-genomic RNA and hepatitis B core-related antigen reductions at week 4 predict favourable hepatitis B surface antigen response upon long-term nucleos(t)ide analogue in chronic hepatitis B

Lung-Yi Mak[1,2,*], Danny Wong[1,2,*], Alison Kuchta[3], Martina Hilfiker[4], Aaron Hamilton[3], Ning Chow[1], XianHua Mao[1], Wai Kay Seto[1,2], and Man-Fung Yuen[1,2]

Background/Aims: We investigated the dynamics of serum HBV pre-genomic RNA (pgRNA) and hepatitis B core-related antigen (HBcrAg) in patients receiving nucleos(t)ide analogues (NAs) and their predictability for favourable suppression of serum hepatitis B surface antigen (HBsAg).

Methods: Serum viral biomarkers were measured at baseline, weeks 4, 12, 24, 36, and 48 of treatment. Patients were followed up thereafter and serum HBsAg level was measured at end of follow-up (EOFU). Favourable HBsAg response (FHR) was defined as ≤100 IU/mL or HBsAg seroclearance upon EOFU.

Results: Twenty-eight hepatitis B e antigen (HBeAg)-positive and 36 HBeAg-negative patients (median, 38.2 years old; 71.9% male) were recruited with median follow-up duration of 17.1 years (interquartile range, 12.8–18.2). For the entire cohort, 22/64 (34.4%) achieved FHR. For HBeAg-positive patients, serum HBV pgRNA decline at week 4 was significantly greater for patients with FHR compared to non-FHR (5.49 vs. 4.32 log copies/mL, respectively; P=0.016). The area under the receiver-operating-characteristic curve (AUROC) for week 4 HBV pgRNA reduction to predict FHR in HBeAg-positive patients was 0.825 (95% confidence interval [CI], 0.661–0.989). For HBeAg-negative patients, instead of increase in serum HBcrAg in non-FHR patients, FHR patients had median reduction in HBcrAg at week 4 (increment of 1.75 vs. reduction of 2.98 log U/mL; P=0.023). The AUROC for week 4 change of HBcrAg to predict FHR in HBeAg-negative patients was 0.789 (95% CI, 0.596–0.982).

Conclusions: Early on-treatment changes of serum HBV pgRNA and HBcrAg at 4 weeks predict HBsAg seroclearance or ≤100 IU/mL in NA-treated CHB patients upon long-term FU. **(Clin Mol Hepatol 2023;29:146-162)**

Keywords: Chronic hepatitis B; Hepatitis B core antigen; Hepatitis B e antigen; Viremia; Treatment outcome

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Editorial

New biomarkers of hepatitis B virus (HBV) infection: HBV RNA and HBV core-related antigen, new kids on the block?

Young-Suk Lim

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Some complexities of diabetes and the heart

Patients with diabetes are at greater risk of coronary artery disease, including severe and diffuse coronary disease, than their peers without diabetes. That's straight and simple. But there the simplicity ends. Patients with diabetes have comorbidities that contribute to the development of coronary artery disease, including chronic kidney disease, obesity (often with obstructive sleep apnea), hypertension, and dyslipidemias. An individual may have none or all of these shared cardiac risk factors. Successful treatment of some of these comorbidities can reduce the risk of coronary and cardiovascular events, and current guidelines call for aggressive management of blood pressure and lipid levels as well as treatment of proteinuria in an effort to reduce progression of kidney disease.

Diabetes is defined by the presence of hyperglycemia or an elevated level of glycosylated proteins, its biochemical footprint. And for 100 years (insulin was first administered in 1922), the control of blood glucose levels has been the target of diabetic therapies. Control of blood glucose levels results in reduced microvascular complications, but reduction of the hemoglobin A1c level has not been uniformly shown to reduce coronary risk. Some controlled studies have instead indicated that aggressive diabetes control may paradoxically increase cardiac events. While it can be argued that some events may have been related to hypoglycemic stress, specific drugs may also play a contributory role.

There are many drugs now available that lower the blood glucose. Many share the ability to increase insulin levels and have efficacy in treating type 2 diabetes. Other drugs have unique biologic mechanisms of action that lower blood glucose without relying entirely on insulin for their effect. They are uniquely different in biochemical structure and thus, not surprisingly, differ in their off-target pharmacologic effects. Subanalyses of clinical trials and observational studies led to the hypothesis that different diabetes drugs have different effects on cardiovascular outcomes, with some contributing to cardiovascular morbidity. Although this was contentious for a while, and total clarity is still not apparent for every drug, it led the US Food and Drug Administration to mandate that clinical trials of new diabetes medications need to include cardiovascular outcome data. And we now have a lot of information on the cardioprotective effects of the sodium-glucose cotransporter 2 inhibitors, even in patients without diabetes.

But our patients with diabetes often have comorbidities that can independently contribute to cardiovascular morbidity, and those comorbidities need to be treated—with more drugs. What about off-target effects of those medications that are demonstrably effective at reducing cardiac

In this issue of the *Journal*, Dr. Byron Hoogwerf presents a comprehensive discussion of statin use and diabetes risk,[1] contributing clinical and data-enriched context to the relationship between statins and diabetes. He provides us with concrete guidance from his perspective as an experienced clinical diabetologist and trialist as to what we can say to patients and how we can sort out this therapeutic conundrum. It is well worth the read.

As we await the snow in Cleveland, on behalf of the entire *CCJM* editorial team, I wish us all a healthy, much kinder, and peaceful 2023.

XBB.1.5 is highly transmissible and immune evasive
countries.

What to know about Omicron XBB.1.5

LAUREN VOGEL | JANUARY 6, 2023

What is XBB.1.5?

XBB.1.5 was first detected in the United States in October, where it has quickly overtaken other circulating strains. The subvariant evolved from XBB, a recombinant or fusion of two Omicron variants, which spread widely in Singapore and India this past fall.

XBB.1.5 now accounts for more than 40% of new COVID-19 cases in the U.S., including 75% of those in the northeast of the country, up from just 1.3% only a month ago. Hospitalizations are also trending upward, although it's still unclear how much that's related to the new subvariant versus recent holidays.

"We haven't seen a variant that's taken off at that speed," Pavitra Roychoudhury, director of Covid-19 sequencing at the University of Washington School of Medicine's virology lab, told *CNN*.

XBB.1.5 has since been identified in more than 25 countries, including Canada. As of mid-December, the federal government identified XBB.1.5 in 0.6% of a thousand or so genomic tests conducted across the country.

However, because COVID-19 testing has dropped off in most jurisdictions, it's difficult to chart the spread of the new subvariant.

As of early January, the British Columbia Centre for Disease Control had detected at least five cases of XBB.1.5, while the health ministries for Alberta, Manitoba, an
Ontario were unable to say whether the subvariant is circulating in those provin

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XBB.1.5 hasn't shown up yet in wastewater testing in Canada's capital, but the overall prevalence of SARS-CoV-2 spiked over the holidays from 20% of the pandemic peak seen this time last year to nearly 50%, according to researchers at the University of Ottawa.

Is XBB.1.5 more contagious?

While data on XBB.1.5 are limited, the World Health Organization says the new subvariant appears to have a marked "growth advantage" making it more transmissible than other circulating strains of SARS-CoV-2.

While XBB had a mutation that helped it evade immunity but hampered its ability to infect cells, XBB.1.5 has further evolved to bind more tightly to cells while continuing to dodge the body's immune defences, allowing it to spread more easily.

American scientists estimate that every person infected with XBB.1.5 will pass it on to 1.6 other people – an effective reproductive rate that's roughly 40% higher than the next most contagious variant.

Newer Omicron variants also attach to cells in the upper airways versus deeply in the lungs, meaning the virus doesn't need to travel as far to cause infection, according to B.C. Provincial Health Officer Bonnie Henry.

Is XBB.1.5 more dangerous?

Like the United States, B.C. has seen a recent uptick in hospitalizations due to COVID-19, but Henry told reporters this is due to more people being infected rather than a more virulent strain.

So far, XBB and its sublineages don't appear to cause more severe disease than other Omicron variants. But as a more transmissible and immune evasive strain, XBB.1.5 could still drive increases in hospitalizations and deaths as more people overall are infected and reinfected.

Do vaccines and treatments work against XBB.1.5?

Do vaccines and treatments work against XBB.1.5?

Early research suggests XBB and its sublineages are more immune evasive than other variants, undercutting the protection provided by vaccines, past infections, and antibody treatments.

In one small study of 35 people published in the *New England Journal of Medicine*, neutralizing antibody levels against newer Omicron subvariants including XBB were 12 to 26 times lower than for the original strain of SARS-CoV-2 in people who had received a bivalent booster. However, the bivalent booster still appeared to offer some benefit, as neutralizing activity was even lower in people who had not received the updated vaccine.

In another recent study, researchers at Columbia University tested BQ and XBB subvariants against 23 monoclonal antibody treatments, as well as antibodies from people who previously had COVID-19, those who received the original and bivalent vaccines, and those who were both previously infected and vaccinated.

The results, published in *Cell*, showed that both BQ and XBB subvariants are "completely resistant" to current monoclonal antibody treatments and demonstrate a dramatically increased ability to evade neutralizing antibodies, even in people who received the bivalent mRNA booster.

Tumour Review

Redefining cancer of unknown primary: Is precision medicine really shifting the paradigm?

Timothée Olivier [a,*], Eugenio Fernandez [a], Intidhar Labidi-Galy [a,b,c], Pierre-Yves Dietrich [a,b,c], Veronica Rodriguez-Bravo [d], Giulia Baciarello [e], Karim Fizazi [f,1], Anna Patrikidou [g,h,1]

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A B S T R A C T

The concept of Cancer of Unknown Primary (CUP) has evolved with the advent of medical oncology. CUP can be difficult to diagnose and represents 2 to 5% of new cancers, therefore not exceptionally rare. Within CUPs can be identified a subset of favourable prognosis tumours, however the vast majority of CUP patients belongs to a poor prognosis group.

CUP features significant oncological challenges, such as unravelling biological and transversal issues, and most importantly, improving patient's outcomes. In that regard, CUP patients' outcomes regrettably showed minimal improvement for decades and CUP remains a cancer group of very poor prognosis.

The biology of CUP has two main hypotheses. One is that CUP is a subgroup of a given primary cancer, where the primary is present but cannot be seen due to its small size. The other, the "true" CUP hypothesis, states that CUP share features that make them a specific entity, whatever their tissue of origin. A true biological signature has not yet been described, but chromosomal instability is a hallmark of poor prognosis CUP group.

Precision oncology, despite achieving identifying the putative origin of the CUP, so far failed to globally improve outcomes of patients. Targeting molecular pathways based on molecular analysis in CUP management is under investigation. Immunotherapy has not shown ground-breaking results, to date. Accrual is also a crucial issue in CUP trials.

Herein we review CUP history, biological features and remaining questions in CUP biology, the two main approaches of molecular oncology in CUP management, in order to draw perspectives in the enormous challenge of improving CUP patient outcomes.

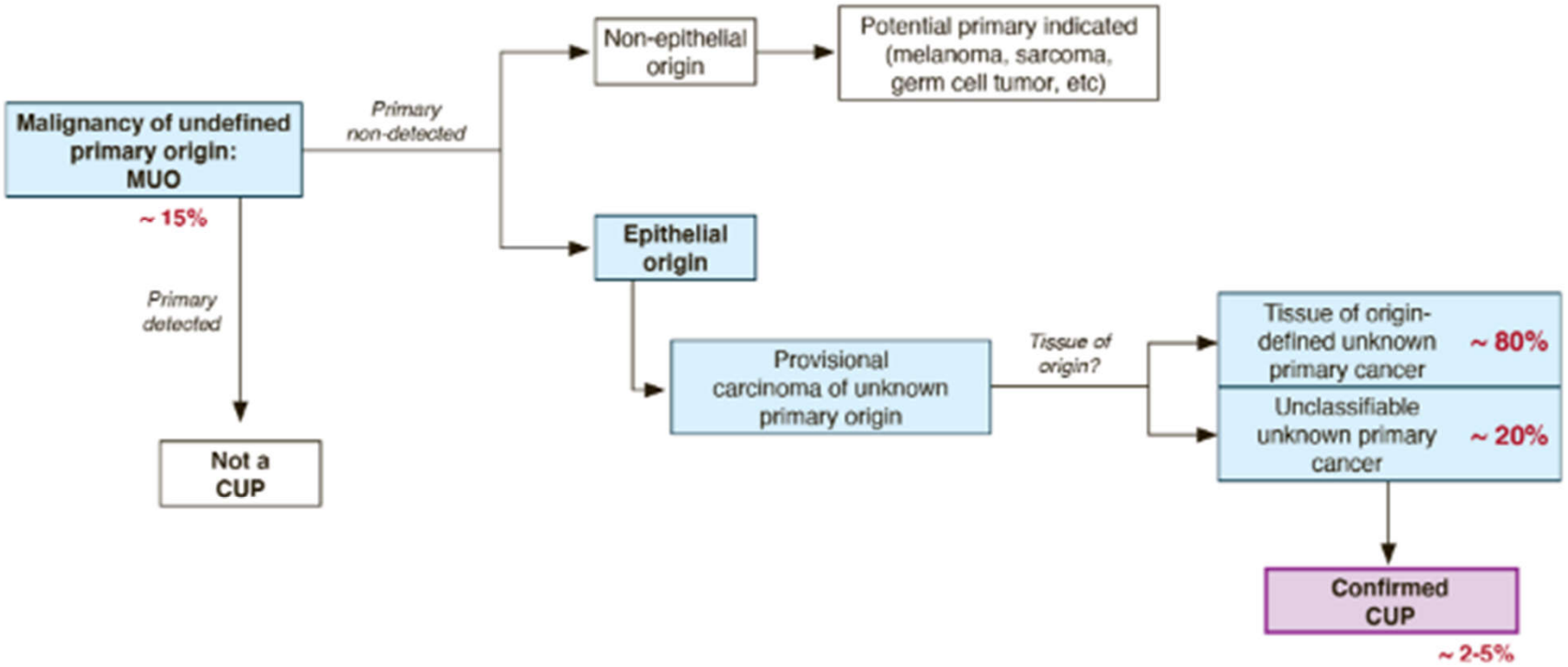
Malignancy of undefined primary origin: MUO
~ 15%
Primary detected
Not a CUP
Primary non-detected
Non-epithelial origin
Potential primary indicated (melanoma, sarcoma, germ cell tumor, etc)
Epithelial origin
Provisional carcinoma of unknown primary origin
Tissue of origin?
Tissue of origin-defined unknown primary cancer
~ 80%
Unclassifiable unknown primary cancer
~ 20%
Confirmed CUP
~ 2-5%

Fig. 1.

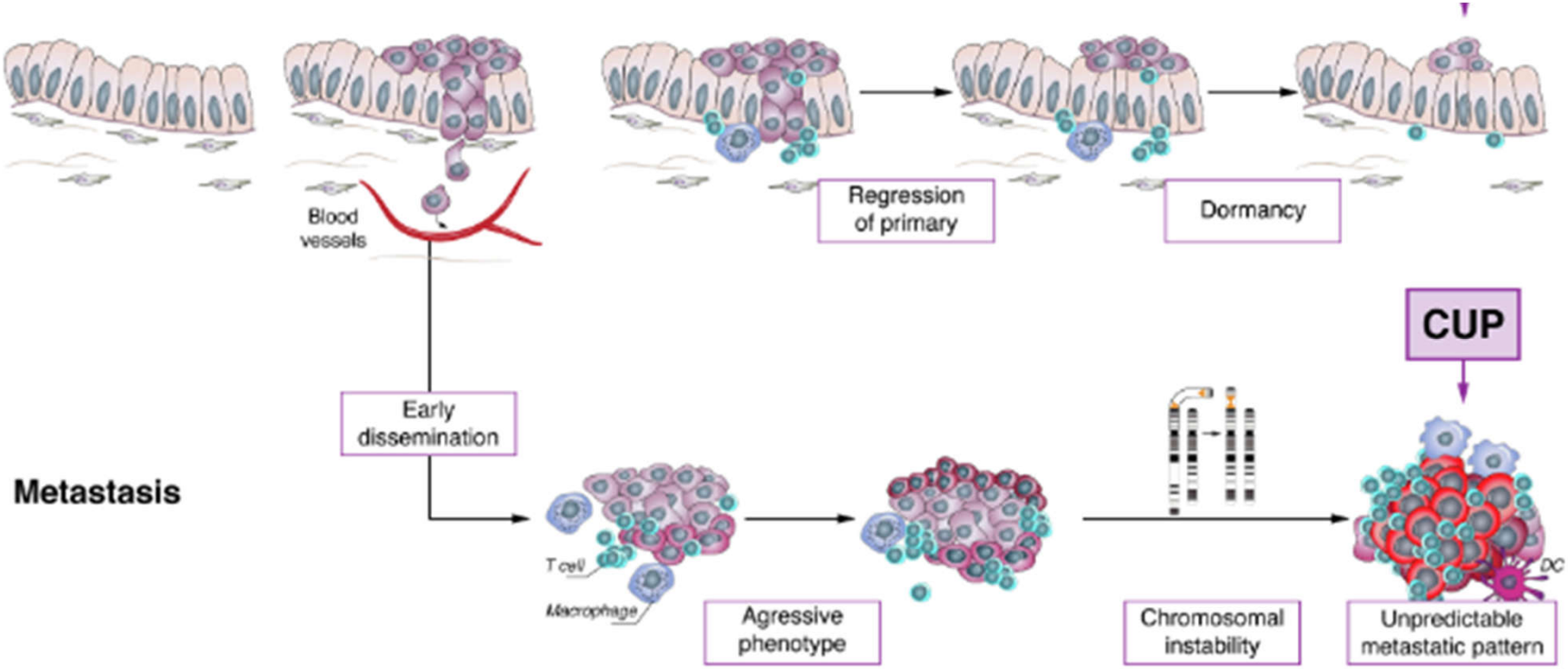

Fig. 2.

ıe future as an important diagnostic marker as well as a targetable axis ı these types of tumours.

enomic alteration in CUPs

Several studies retrospectively examined the genomic landscape of UPs through DNA profiling (Table 2).

targetable shows wide discrepancy according to studies, varying from 15% to 85% [57,60,63–69]. Such analyses highlight the need to keep a high level of stringency in defining a "clinically relevant" alteration, which should go beyond bio-plausibility, and ideally rely on improved clinical outcomes associated with targeting such alterations, but also access to relevant approved targeted agents in diverse healthcare settings.

Conclusion

CUPs could be viewed as the quintessence of oncology, with many transversal biological issues, challenges that are found across oncology in general, but crucially with urgently needed answers to improve patient's clinical outcomes. Although a highly heterogeneous group of cancers, CUPs can be categorised in two very distinct groups, at levels of biology, clinical presentation, treatment strategies and prognosis. The first group of specific subset CUPs behave closely like their counterpart known primaries, and benefit from same treatment strategies leading to same outcomes. Whether molecular profiling can enlarge this group of good-prognosis, specific-subset CUPs is an interesting point that remains to be seen.

The vast majority of CUP patients belongs to the unfavourable, non-specific subset CUP group. They present with very poorly differentiated tumours, high chromosomal instability, aggressive and unpredictable metastatic pattern, and poor prognosis. A true "molecular signature" has not yet been identified, yet chromosomal instability seems to be a hallmark of unfavourable CUPs. The main issue pertains to this unfavourable subgroup of CUP patients, where almost no improvement has been achieved for decades. Recent randomised trials have shown that tissue of origin classifiers used to guide treatment do not modify outcomes. Molecular analysis in order to find matched targeted therapies could probably select a proportion of patients that could benefit from these treatments, but prospective evidence is awaited. Within this context, whether immune checkpoint inhibitors could be beneficial remains an ongoing question.

A promising area of research focus could be the possibility of identifying a "feature signature" within the unfavourable group of CUPs that could be found in an "-omics" levels and could transcend the tissue of origin pattern (metabolism, microenvironment, non-coding DNA region, epigenetics). How to target chromosomal instability is also of major interest, as well as how to combine treatment to prevent acquired resistance.

THE END