Section 1: Application Summary

Name of Product	***Resistance****Plus*® GC
Australian launch date	**February 15th 2019**
Products used in (please select)	✔ diagnosis prevention treatment management
Contact details	**See below**

Your details

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Executive Summary: [200 words max.] NB Executive Summary must be suitable for use in Award promotion

Resistance*Plus*® GC is a diagnostic test detecting both the sexually transmitted infection (STI) *N. gonorrhoeae* (gonorrhoea) and gene sequences of the bacteria associated with susceptibility to ciprofloxacin, a previously used front-line antibiotic treatment. Currently, ceftriaxone–a painful intramuscular injection–combined with azithromycin, is the front-line treatment for gonorrhea. However, ceftriaxone represents one of the last remaining antibiotics used for multi-drug-resistant infections and needs to be utilized sparingly so as not to increase resistance to the drug. Already, there are strains of gonorrhea that are resistant to this treatment.
Based on gonorrhoea surveillance data, ***Resistance****Plus* GC could enable doctors to confidently and cost-effectively treat up to 70% of gonorrhea infections with a single oral dose of ciprofloxacin, because the test establishes disease susceptibility to ciprofloxacin prior to prescribing.
Resistance*Plus* GC is the first commercially available molecular test providing ciprofloxacin susceptibility information and will promote antibiotic stewardship of our last-line therapies. An Australian wide study (GRAND 2 – funded by NHMRC) is underway to assess the impact of ***Resistance****Plus* GC on prescription practices and overall patient cure rates. Study outcomes may impact national guidelines and lead to the inclusion of Resistance Guided Therapy for gonorrhoea management.

Section 2: Product Details

Describe the technology [300 words max.]

Resistance*Plus*® GC is a molecular clinical diagnostic (qPCR) test that detects the sexually transmitted infection (STI) *Neisseria gonorrhoeae* (gonorrhoea), along with genetic markers linked to ciprofloxacin antibiotic susceptibility. It uses proprietary ***Plex****Zyme*®[1,2] and ***Plex****Prime*®[3] technologies that have enhanced multiplex performance compared with other probe-based tests. This allows for detection of the pathogen and multiple gene targets in a single well test, a desirable quality to support easy laboratory workflow. ***Resistance****Plus* GC is CE-IVD marked and TGA approved for use across Europe, U.K., Australia, and New Zealand, and recently received Breakthrough Designation status from the U.S. FDA - expediting the path towards FDA clearance as we prepare for clinical trials in the U.S.
Plex*Zyme* technology is the driver of ***Resistance****Plus* GC and offers high performance and reliable qPCR detection required for clinical diagnostic applications. ***Plex****Zyme* enzymes are catalytic DNA complexes which assemble in the presence of target and cleave universal probes (see Figure 1a). An active ***Plex****Zyme* is made up of two DNA oligonucleotide components called partial enzymes or “partzymes”. Each partzyme comprises only part of a catalytic core flanked by a sensor arm which binds to a target sequence, and a substrate arm which binds to a universal probe. Partzymes are inherently inactive; however, when bound adjacently on a target, they form an active ***Plex****Zyme* (see Figure 1b). ***Plex****Zyme* enzymes catalyse the

cleavage of universal probes, resulting in fluorescence signal that can be monitored in real time (see Figure 1c).[1,2] ***Plex****Prime* is a novel method for nucleic acid amplification that creates amplicons which are distinctly different from the parent sequence (see Figure 2).[3]
Through use of innovative ***Plex****Prime* and ***Plex****Zyme* technologies, ***Resistance****Plus* GC achieves multiplex detection of the pathogen and multiple gene targets in a single test with high sensitivity and specificity.

What health problem is the technology addressing and how does it address the problem? [300 words max.]

The rise in antibiotic-resistant gonorrhoea (GC) is one of the biggest challenges to public health and is rated high in the World Health Organisation priority pathogen list.[4] Symptoms include pain when urinating, and discharge or bleeding from the infected area. Untreated gonorrhoea can cause serious and permanent health problems and infertility in both women and men. Untreated gonorrhoea in new-born babies who contract it from the mother during childbirth can lead to permanent blindness.
While new antibiotics are still in development, urgent action is needed to improve management strategies to control gonorrhoea, including improved diagnostics and better utilization of existing drugs. Broad recommendations to utilize specific treatments in traditional syndromic management practices for STIs requires the antibiotic to have >95% efficacy.[5] Ciprofloxacin, a single-dose oral antibiotic, was in broad use for treatment of gonorrhoea, but as resistance rates started to rise above the 5% cut-off, guidelines were changed to a dual-therapy azithromycin and ceftriaxone treatment, the latter of which is a painful intra-muscular injection.[6] Gonorrhoea infections that do not respond to this recommended front-line dual therapy have been reported in the UK[7] and Australia,[8] and the term 'extensively drug-resistant ' (XDR) is now being used for strains exhibiting high-level azithromycin resistance in addition to ceftriaxone and most other alternative antimicrobials.[9]
The availability of ***Resistance****Plus* GC, which can diagnose infection and detect resistance/susceptibility markers, will enable older treatments such as ciprofloxacin to be 'recycled' into use. The latest surveillance data from around the globe (Figure 3) suggests that over half the reported gonorrhoea infections are susceptible to ciprofloxacin, meaning these cases could be treated with a simple oral antibiotic.[10-13] ***Resistance****Plus* GC will be an effective tool to support antimicrobial stewardship and help move prescription practices away from syndromic management towards Resistance Guided Therapy for more targeted and effective patient care.

What other products are currently available to address this issue and how does this technology differ from and/or improve on existing technology? [300 words max.]

Resistance*Plus*® GC is the first commercially available molecular test of its kind. ***Plex****Zyme*®[1,2] and ***Plex****Prime*®[3] technologies overcome known challenges of gonorrhoea diagnostics, particularly in relation to pharyngeal samples that may contain non-pathogenic *Neisseria* species that can interfere with the reaction.[14]
Non-molecular methods for assessing antimicrobial susceptibility include laboratory culture. This approach, although relatively inexpensive and simple to perform, has a longer turn-around time limiting clinical utility. Culture also requires a viable organism, which is a challenge when dealing with samples requiring long distance travel from remote clinics.
Sexual Health Clinicians and gonorrhoea surveillance experts worldwide have welcomed the availability of ***Resistance****Plus* GC:

"The development of this test represents a step in the right the direction for dealing with the gonorrhoea resistance problem. For the first time it will provide clinicians with treatment options other than ceftriaxone for treating gonorrhoea, and in doing so will make better use of currently-available antibiotics such as ciprofloxacin. This is important as we are fast running out of antibiotics for treating gonorrhoea." Associate Professor David Whiley, a leading N. gonorrhoea researcher from Pathology Queensland and the University of Queensland, UQ Centre for Clinical Research.

"The ResistancePlus GC test is the first innovation in gonorrhea treatment in decades. With the continued spread of multi-drug resistant gonorrhea, this test can make a real difference." Dr. Jeffrey Klausner, Professor of Medicine and Public Health at David Geffen School of Medicine and Fielding School of Public Health, University of California, Los Angeles.

"It's great to see novel molecular diagnostics moving beyond just a positive/negative capability - providing results that help manage patients more effectively by enabling tailored treatment," Dr. John White, Sexual Health Physician in the UK and Editor-in-Chief of the *International Journal of STDs & AIDS*.

Having regard to the consumer's quality of life, does the product provide a balance between invasiveness

and efficacy? [300 words max.]

Diagnosis supported by ***Resistance****Plus*® GC is non-invasive, requiring a simple urine, genital or rectal swab sample from the patient. ***Resistance****Plus* GC has 96.9% sensitivity and 99.7% specificity for detection of gonorrhoea and 100% sensitivity and 98.6% specificity for susceptibility markers.[15] The tests on clinical samples returned 100% sensitivity and specificity data for mutation detection indicating resistance to ciprofloxacin, thus the assay could be confidently used for informing ciprofloxacin treatment.

Given that the current empiric treatment for gonorrhoea involves a painful intramuscular injection of ceftriaxone, the alternative offered through the use of ***Resistance****Plus* GC – a single oral dose of ciprofloxacin – would be a welcome choice for any patient. Patients that have gonorrhoea strains that are susceptible to ciprofloxacin can avoid this painful injection, plus the need to use painkillers at the time of treatment.

The test also benefits healthcare professions and the overall costs of healthcare. Injection of ceftriaxone requires skilled nurses and clinic real estate to administer the treatment. Ciprofloxacin can be prescribed remotely and consists of a single oral tablet. Ciprofloxacin is also available as a generic medicine thus representing additional cost savings to the public health network.

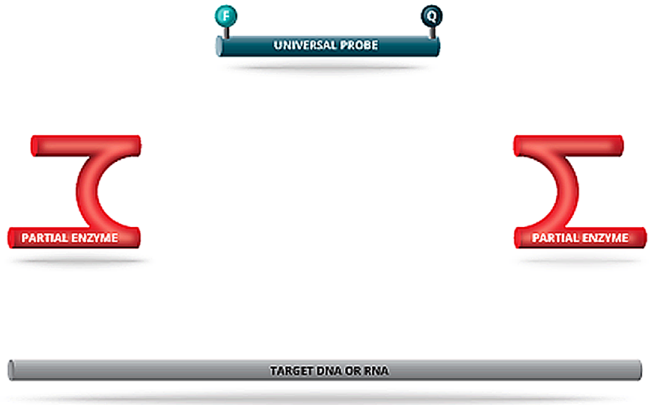
Resistance*Plus* GC provides valuable information to guide treatment decisions away from the last-line therapies. Management guidelines for gonorrhoea published by the British Association for Sexual Health and HIV (BASHH) in the U.K. are the first to formally recognise the need for antimicrobial stewardship of last-line treatments, recommending susceptibility testing and preferential use of ciprofloxacin for gonorrhoea infections.[16] ***Resistance****Plus* GC will provide clinicians with diagnostic information on the infective agent as well as the resistance profile, enabling Resistance Guided Therapy for gonorrhoea infections. Use of ***Resistance****Plus* GC would assist in conserving use of last line antimicrobials and ultimately reduce the spread of antimicrobial-resistant gonorrhoea in the community.

Include scientific evidence to support the claims. This may include published data, unpublished scientific data, results of clinical trials and/or patient feedback. Photographs may be submitted. Product samples will not be accepted.

Figures:

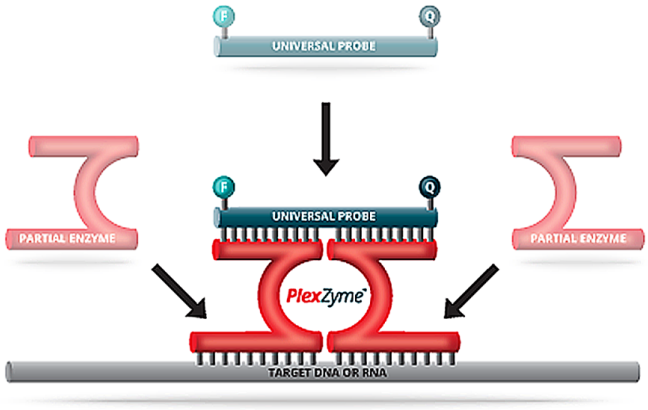
Figure 1

A



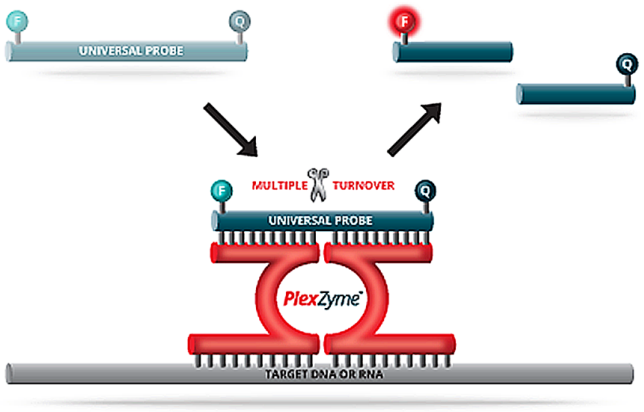
An active PlexZyme® is made up of two DNA oligonucleotide components called partial enzymes or "partzymes". Each partzyme comprises only part of a catalytic core flanked by a sensor arm which binds to a target sequence, and a substrate arm which binds to a universal probe.

B



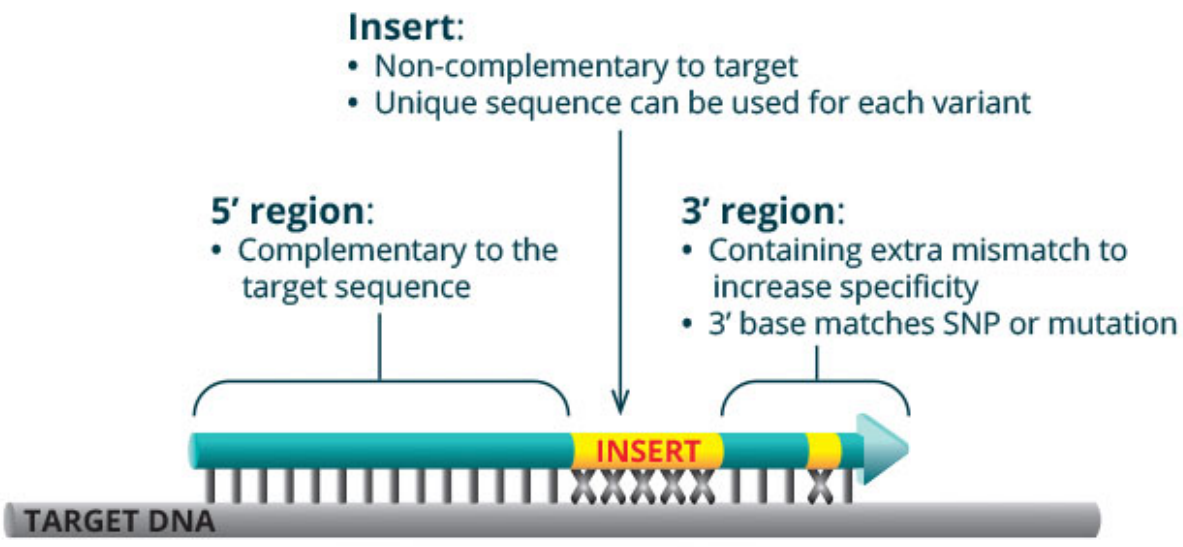
Partzymes are inherently inactive; however, when bound adjacently on a target, they form active PlexZyme®.

C



PlexZymes® catalyse the cleavage of universal probes, resulting in fluorescence signal that can be monitored in real time.

Figure 2



The PlexPrimer® is composed of three regions - the 5' region anchors the primer to a particular location in the target, the 3' region selectively amplifies the target sequence of interest and the Insert lies between the 5' and 3' regions, acting as a bridging structure which both (a) inserts target-independent sequence into the resulting amplicon and (b) increases the selective pressure of the 3' region.

Figure 3: *Neisserria gonorrhoeae* (GC) resistance data (% of total isolates) from national sureveillance programs. (a) European Gonococcal Antimicrobial Surveillance Programme,[17] (b) Australian Gonococcal Surveillance Programme,[10] the (c) New Zealand Public Health surveillance,[11] and the (d) Gonococcal Isolate Surveillance Project, United States.[12] (e) data indicate reduced susceptibility to ceftriaxone.

	Cipro-floxacin resistance	Azithro-mycin resistance	Ceftri-axone resistance	% Susceptible to Cipro-floxacin
Austria[a]	78%	1%	0	22
Belgium[a]	53%	0%	0	47
Cyprus[a]	88%	25%	0	12
Denmark[a]	53%	7%	0	47
France[a]	53%	0%	0	47
Germany[a]	49%	2%	0	51
Greece[a]	71%	29%	0	29
Hungary[a]	73%	0%	0	27
Iceland[a]	40%	0%	0	60
Italy[a]	50%	0%	0	50
Latvia[a]	26%	16%	0	74
Malta[a]	40%	0%	0	60
Netherlands[a]	36%	2%	0	64
Norway[a]	80%	11%	0	20
Portugal[a]	46%	19%	0	54
Slovakia[a]	47%	0%	0	53
Slovenia[a]	61%	0%	0	39
Spain[a]	65%	9%	4%	35
Sweden[a]	56%	10%	0	44
UK[a]	26%	0%	0	74
Australia[b]	27%	3%	1.8%[e]	73
New Zealand[c]	32%	2%	2.6%[e]	68
USA[d]	30%	2.5%	0.8%[e]	70

References:
1. Mokany E, Tan YL, Bone SM, Fuery CJ, Todd AV. MNAzyme qPCR with superior multiplexing capacity. Clin Chem. 2013 Feb;59(2):419-26. doi: 10.1373/clinchem.2012.192930. Epub 2012 Dec 11.
2. Mokany E, Bone SM, Young PE, Doan TB, Todd AV. MNAzymes, a versatile new class of nucleic acid enzymes that can function as biosensors and molecular switches. J Am Chem Soc. 2010 Jan 27;132(3):1051-9. doi: 10.1021/ja9076777.

3. Tan LY, Walker SM, Lonergan T, Lima NE, Todd AV, Mokany E. Superior Multiplexing Capacity of PlexPrimers Enables Sensitive and Specific Detection of SNPs and Clustered Mutations in qPCR. PLoS One. 2017 Jan 23;12(1):e0170087. doi: 10.1371/journal.pone.0170087. eCollection 2017.
4. WHO publishes list of bacteria for which new antibiotics are urgently needed. 27 February 2017. Found at: https://www.who.int/news-room/detail/27-02-2017-who-publishes-list-of-bacteria-for-which-new-antibiotics-are-urgently-needed
5. Guidelines for the Management of Sexually Transmitted Infections. World Health Organization 2003.
6. WHO Guidelines for Treatment of Neisseria gonorrhoeae. World Health Organization 2016.
7. UK case of Neisseria gonorrhoeae with high-level resistance to azithromycin and resistance to ceftriaxone acquired abroad - Health Protection Report Advanced Access Report Volume 12 Number 11. Public Health England 2018.
8. Murphy, B. Multi-drug resistant gonorrhoea. Australian Government Department of Health 2018.
9. Extensively drug-resistant (XDR) Neisseria gonorrhoeae in the United Kingdom and Australia. European Centre for Disease Prevention and Control 2018.
10. Harris, S. R. et al. Public health surveillance of multidrug-resistant clones of Neisseria gonorrhoeae in Europe: a genomic survey. Lancet Infectious diseases 18, 758–768 2018.
11. Lahra, M. M. Australian Gonococcal Surveillance Programme annual report, 2015. Australian Government Department of Health 2015.
12. Heffernan, H., Woodhouse, R. & Williamson, D. Antimicrobial resistance and molecular epidemiology of Neisseria gonorrhoeae in New Zealand, 2014-15. The New Zealand Ministry of Health 2015.
13. Kirkcaldy, R. D. et al. Antimicrobial Susceptibility Surveillance — The Gonococcal Isolate Surveillance Project , 27 Sites , United States , 2014. Centers for Disease Control and Prevention (CDC) 65, 2016.
14. Ebeyan S, Windsor M, Bordin A, Mhango L, Erskine S, Trembizki E, Mokany E, Tan LY, Whiley D, GRAND2 Study Investigators, Evaluation of the ResistancePlus GC (beta) assay: a commercial diagnostic test for the direct detection of ciprofloxacin susceptibility or resistance in *Neisseria gonorrhoeae*, J Antimicro Chemo, Volume 74, Issue 7, July 2019, Pages 1820–1824.
15. ResistancePlus® GC Instructions for use
16. Fifer et al. British Association for Sexual Health and HIV national guideline for the management of infection with *Neisseria gonorrhoeae* (2019).
17. Eyre DW et al. Euro Surveill. 2019;24(10):pii=1900147.

Section 3: Declaration

I certify that the information provided in this application is accurate and that the company accepts the Rules of the Award. Representative/s of the company will participate in promotional activities relating to the Award.

Name: COLIN DENVER *Position:* CEO

Signature of the CEO/Authorised Representative: _____

Date: 26 / 6 / 2019

Please send your application to MTAA Secretariat – Kerrin Rennie Award

CLOSING DATE: **26 JULY 2019**