

QML PATHOLOGY

newsletter February 08

>>Warfarin Therapy Update

Dr Sue Moreton, Pathologist, Haematology Department

Warfarin therapy is used for many indications, most of which are increasing in prevalence. This combined with the ageing population, results in an overall increase of the number of patients on warfarin in our community.



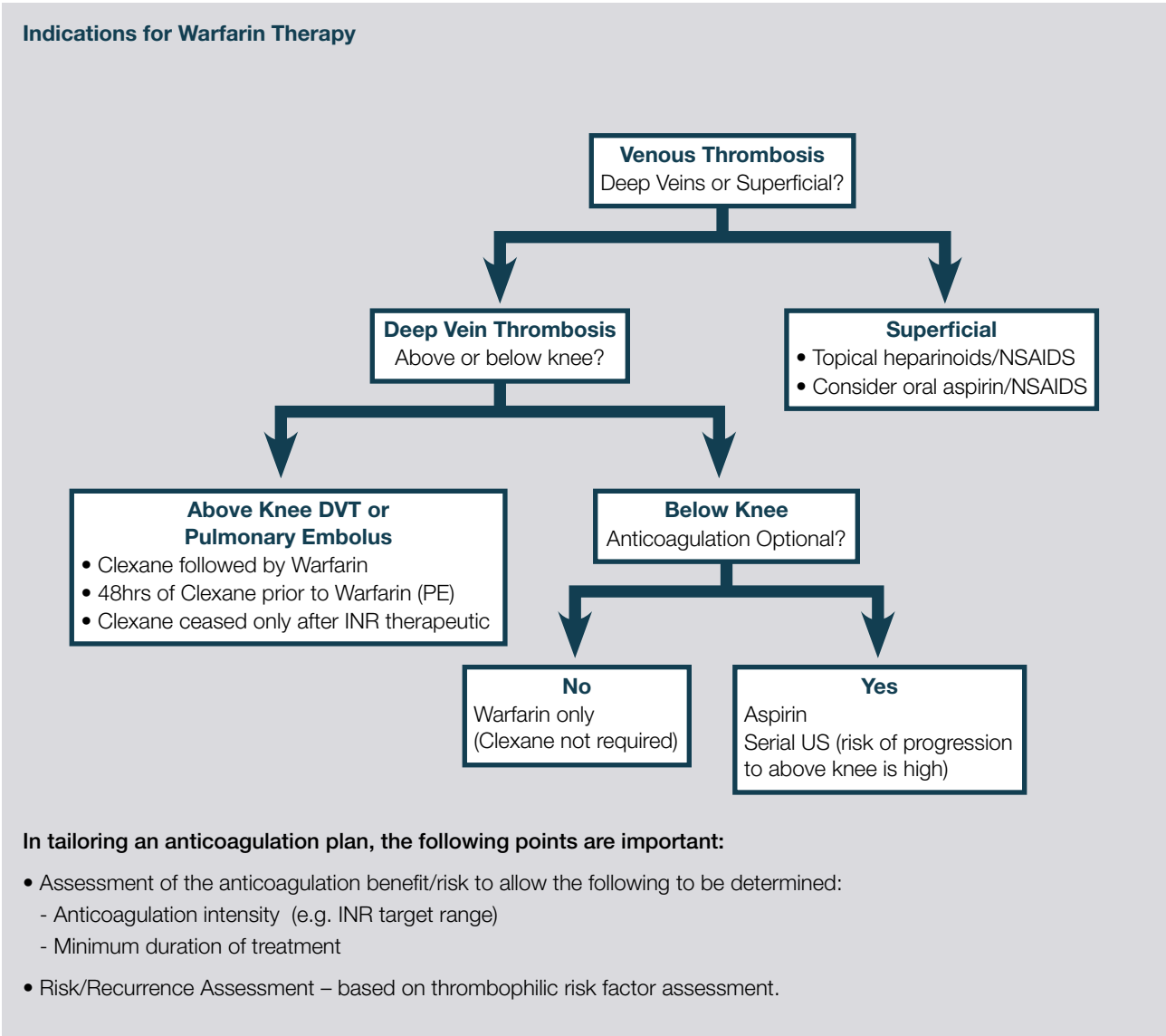
>> Warfarin Therapy Update

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QML Pathology's warfarin service currently tends to over 18,000 patients, and provides doses for between 1600 and 3800 patients per day, giving us one of the largest services in the world.

The decision to treat with anticoagulants requires an assessment of:

Potential Benefits		Potential Risks
Prevention of extension of DVT Prevention of Embolus Reduction in post-phlebotic symptoms	VERSUS	Bleeding - Local - Distant



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Initiating Warfarin Therapy

When initiating warfarin therapy the loading of doses should be avoided as it causes early procoagulant effects, and oscillating INRs that take longer to stabilise than a steady increase in dose.

QML Pathology uses a formula that factors in each patient's age and weight to derive an individual dose. The formula gives us the Estimated Maintenance Dose (EMD) as demonstrated below.

$$\text{EMD} = \text{square root of } \frac{[\text{weight} \times (100 - \text{age})]}{100}$$

E.g. for a 75kg, 60 year old

$$\text{EMD} = \sqrt{\frac{[75 \times (100 - 60)]}{100}} = \sqrt{[75 \times 0.4]} = 5.4\text{mg}$$

5mg is the recommended starting dose; however, the choice of starting dose may need to be modified for a number of reasons, such as the patient's current medications, which may interact with warfarin (see upcoming section). For example, you may wish to start a patient with AF on Lipitor on 4mg. If the patient is being warfarinised for an acute VTE, there is often an increase in acute phase factors causing an element of resistance to anticoagulation. In this case, you may wish to round up the starting dose to 6mg. As liver disease usually causes reduced warfarin requirement you should divide the EMD by the baseline (pre-anticoagulation) INR to give the correct EMD.

As warfarin is not excreted via the kidneys, renal function is not a component of this equation. However, if clexane is

being used, renal function should be measured for the use of this drug, and dose adjustment made if eGFR < 30ml/min.

Graph 1 (below) illustrates the common phases in INR levels in a patient commenced and maintained on their EMD (target INR range of 3.0 - 4.0), for a two-week period without any change in dose.

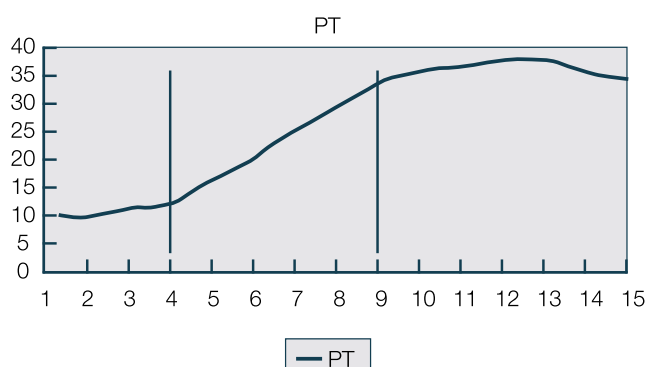
Intervals of Testing

Warfarin has a half-life of 20 - 60 hours (avg of 40 hrs); with changes in dose taking 2 half-lives to affect serum levels. For this reason INRs are best checked after 2 - 4 days. The Vitamin K dependent factors have half-lives varying from 6 hours for Factor VII and up to 4 days for Prothrombin (Factor II). Accordingly, during the initial phase of warfarinisation the INR may show little movement in the first 2 - 4 days until all Vitamin K dependent factors start to fall. Sometimes an INR, if it has been very high, will be measured sooner to ensure it is coming down, but it should be remembered that INRs will not be reflective of a new dose if taken sooner than four days after a dose change. The temptation to increase excessively the warfarin dose in this initial 'resistance' period should be resisted.

As patients come into range, their test interval is increased. If they remain in range and without a dose change, their test interval will be progressively increased to a maximum of 12 weeks (if less than 70 years), 10 weeks (if 70-80 years) or 8 weeks (if older than 80 years). If their dose changes or they fall significantly outside of their target range, their test interval will be reduced to ensure their instability does not recur or magnify.

Graph 1:

Common phases in INR levels in a patient commenced and maintained on their EMD (target INR range of 3.0 - 4.0), for a two-week period without any change in dose.



There are 3 main phases:

- i) An initial resistance phase: The INR may not change significantly in the first 2-4 days.
- ii) A response phase: The INR begins to increase at a steady rate.
- iii) A plateau phase: The INR stabilises, and will often show a (slight) drop in the tail.

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Range of Target INRs

Indication	INR	Indication	Type valve	RF	INR
AF	2-3	AVR	Bileaflet/Med-tronic Hall	-ve +ve	2-3 2.5-3.5
DVT	2-3	AVR	Starr-Edwards/disc*	+/-ve	2.5-3.5
Extensive DVT	2.5-3	AVR/MVR	Bioprosthesis	-ve	Aspirin
PE - Young	2.5-3.5	MVR	Any	+/-ve	2.5-3.5
PE - Old	2-3	AVR	Bioprosthesis	+ve	2-3
Lupus anticoagulant	2.5-3.5 [†]	MVR	Bioprosthesis	+ve	2.5-3.5

AVR = Aortic Valve replacement; MVR = Mitral Valve Replacement; AF= Atrial Fibrillation; DVT = Deep Venous Thrombosis; PE = Pulmonary Embolism.

* (other than Medtronic Hall)

RF – Risk Factors = include AF, previous thromboembolism, LV dysfunction, and hypercoagulable condition. [†] - depends on strength of anticardiolipin or lupus anticoagulant.

Duration of Warfarin Therapy

Duration of treatment depends of the site of the thrombosis and the risk status of the patient. Those risks include re-thrombosis and bleeding from the warfarin therapy. To enable the former to be evaluated adequately, the patient should be tested for the presence of any inherited or acquired prothrombotic conditions, the most familiar being Factor V Leiden, but there are others more clinically likely to affect the risks to re-thrombosis.

Reversible or Time Limited Factor	Spontaneous (Idiopathic)	Higher Risk	High Risk
Surgery, trauma, pregnancy/ OCP, immobilisation, long haul flight	No cause found	Factor V, PT gene (heterozygous) above with either life threatening thrombosis or thrombosis in unusual site (mesenteric, cerebral vein)	Active malignancy, moderate antiphospholipid syndrome, ATIII def, homozygous or compound heterozygous thrombophilias, recurrent thromboses
3 months	6-12 months	12-24 months	Indefinite

At the completion of the standard period of anticoagulation, decisions need to be made regarding anticoagulation:

- Should anticoagulation be ceased
- Should full anticoagulation continue or
- Should anticoagulation be continued at lower intensity (selected indications)?

For this review the ultrasound (or CT Pulmonary Angiogram) should be repeated and possibly a D-dimer performed. The medical conditions that increase bleeding risk should be considered, as well as any new relevant medications such as aspirin or NSAIDs. As the patient gets older, the prevalence of medical conditions, medications and situations that contribute to the risk of bleeding increase. In younger patients the balance of the risks is often in favour of prevention of thrombosis, but with increasing age and risks of falls, this balance shifts, and the situation must be repeatedly re-evaluated, as there are few firm indications for indefinite warfarin.

Drugs that Interact with Warfarin

Warfarin is metabolised by the Cytochrome P450 system. As such there are many drugs that can cause some change in the INR. However, there are some that have a marked effect and which patients should be warned about. In general, every time a new medication is commenced or one is ceased, the patient should tell the warfarin control centre or their treating doctor, and their INR should be checked. Some medications are notorious for interfering with warfarin. We have compiled a list of the most common and important drugs below.

Drug	Affect on INR	Grade of Affect
Amiodarone	↑	Moderate - Severe
Aspirin	None*	Moderate
Fluconazole	↑	Marked
Most Antibiotics	↑	Moderate
Flucloxacillin	↓ rare increase	Moderate
Keflex	Variable often ↓	Mild - Moderate
Metronidazole	↑	Marked
NSAIDs	↑ also platelet inhibition	Mild - Moderate
Panadol Regular >4/day	↑	Moderate - Severe
Rifampicin	↓	Marked
Statins	↑	Mild - Moderate
Tramal	↑	Moderate
Tegretol	↓	Mild - Moderate

*but increased risk of bleeding via platelet inhibition
[shaded box] = those drugs which decrease INR

>> Warfarin Therapy Update (Cntd.)

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Warfarin Reversal

The warfarin reversal guidelines table is available from the ANZSBT website at the following address:

<http://www.anzsb.org.au/resources/pubs.cfm>

There is a close relationship between bleeding and the INR. The risk of bleeding increases significantly once the INR is > 5. The decision to reverse warfarin depends on the INR, the clinical indications for anti-coagulation and any bleeding that may be present.

In addition to ceasing warfarin, Vitamin K can be administered either orally or parenterally. Although Vitamin K is available as a 10mg tablet, QML Pathology finds smaller doses more useful as 10mg causes warfarin resistance following its administration, which can be problematic in many clinical settings. QML Pathology uses paediatric ampules of Vitamin K, as the dosing is more suitable, even for oral use. To give them orally, the ampule is opened and emptied into water or preferably orange juice, as the taste is not particularly pleasant, and swallowed. The 2mg ampule is used, and the dose is either 1mg or 2mg depending on the starting (and desired finishing) INR and PT. Ampules are available from QML Pathology if the patient is on our monitoring service, or from some pharmacies. Note that the expiry date should be checked before use. Vitamin K must NOT be GIVEN intramuscularly for patients with high INRs, as haematomas will form and Vitamin K can exhibit depot characteristics in these circumstances, such that adsorption is delayed acutely but occurs later and makes subsequent dosing difficult.

You should also consider the possible CAUSES of the high INR. If the cause is known and temporary, like a course of antibiotics, which have now ceased, and the patient was stable before, then you should withhold a dose or two and recommence the old dose. If the cause is a new drug that is continuing (e.g. started on amiodarone), then withhold and lower the dose. If the cause is unknown, then the safest cause is probably to lower the dose, although with mechanical valves, lower doses can be dangerous too.

References and Recommended Reading:

Warfarin Reversal: Consensus guidelines, on behalf of Australasian society of Thrombosis and Haemostasis. Baker R, Coughlin P, Gallus A et al. MJA 2004 Nov; 181(9):492-7.

Duration of anticoagulation following venous thromboembolism: a meta-analysis.

Ost D; Tepper J; Mihara H; Lander O; Heinzer R; Fein A JAMA 2005 Aug 10; 294(6):706-15.

Short-term and mid-term outcome of isolated symptomatic muscular calf vein thrombosis.

Gillet JL; Perrin MR; Allaert FA

J Vasc Surg. 2007 Sep;46(3):513-9. Epub 2007 Jul 30.

ACC/AHA 2006 guideline for the management of patients with valvular heart disease. A report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines. Bonow RO, Carabello BA, Chatterjee K et al. J Am Coll Cardiol Aug; 48(3):e1-148.



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Dr Sue Moreton graduated with her MBBS from the University of Queensland in 1984, completing her residency and subsequent training with the Royal Brisbane, Prince Charles and Mater Hospitals. In 1994 she obtained a dual fellowship of the Royal College of Pathologists and College of Physicians. Dr Moreton did her advanced Haematology training in the USA (1994 -1995) at the M.D. Anderson Cancer Centre in Houston, where she specialised in the diagnosis and management of Leukaemia.

On her return she took up a consultant Clinical Haematologist role at the Mater Hospital, joining the Haematology Department at QML Pathology in a part time capacity in 2003. Taking on a full time position in 2004, Dr Moreton has special interests in haematological malignancy, specifically CLL and myeloma. She is also one of the main advisers to QML Pathology's warfarin dosing service and is available for advice on warfarin management.

Associations

Haematological Society of Australia and New Zealand
Australian and New Zealand Society of Blood Transfusion
American Society of Blood Transfusion
Australian Leukaemia and Lymphoma Study Group

Special Interests

Chronic Lymphocytic Leukaemia
Myeloma
Warfarin Dosing Management
Malignant Haematology

clinical data Feb 08

Infectious Diseases Report - Geographic Distribution - January 2008

ORGANISM	Regions (as per key below)															Total			
	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	Jan	Dec	Nov	Oct
Adenovirus (not typed)	1	3					3			1	2	2		2	1	15	12	8	8
Adenovirus (typing pending)	1	1	1				2				2			1		8	3	2	0
Barmah Forest virus	2	2		2			6		12	3	2	6	2	2	10	49	29	28	12
Bordetella pertussis	1	7	1	1			11		2	1	11	5	1			41	27	34	14
Brucella species		2							1		1					4	0	4	0
Campylobacter jejuni																0	0	0	0
Chlamydia pneumoniae																0	0	0	0
Chlamydia trachomatis, not typed	58	73	13	20	2	2	63		39	17	94	45	5	21	12	464	426	375	200
Coxiella burnetii	1		2						2	1	1	8	3			18	8	14	11
Cryptococcus species							3				1					4	1	3	0
Cytomegalovirus (CMV)	3	9	5	3			12		5	2	13	6	2	1	3	64	56	61	31
Entamoeba histolytica																0	0	0	0
Enterovirus - not typed		1	1										2	1		5	4	5	3
Epstein-Barr virus (EBV)	3	8	5	2			18		8	5	24	16	4	1	2	96	88	94	45
Flavivirus unspecified	2									1	2	1				6	5	5	4
Hepatitis A virus		1	1				2				2					6	3	1	4
Hepatitis B virus	10	4	3				10		1	1	23	3			1	56	46	66	23
Hepatitis C virus	14	42	17	3	3		23		30	4	51	34	8	8	12	249	160	194	86
Hepatitis D virus																0	0	0	0
Hepatitis E virus																0	0	0	0
Herpes simplex Type 1	10	27	10	5	2	1	43		22	10	40	25	4	8	2	209	226	187	74
Herpes simplex Type 2	10	18	8	5			26		17	3	28	17	5	14	6	157	131	137	81
Herpes simplex virus - not typed	3	5		1			7		6	2	11	8		2	2	47	40	26	20
HIV-1	2	1					2				2					7	5	4	2
HTLV-1																0	0	0	0
Influenza A virus		1					6		1			2				10	11	6	9
Influenza B virus												1				1	2	2	0
Legionella species																0	0	0	0
Leptospira species	2											4				6	3	3	2
Measles																	1	0	1
Mumps virus								2	1	1						4	1	1	0
Mycoplasma pneumoniae	2	2					6	1	1	1	3	3	1			20	23	23	18
Neisseria gonorrhoeae	5	6		1			7				9	4		1	1	34	16	17	16
Parainfluenza virus Type 1							1									1	1	1	0
Parainfluenza virus Type 2												1		1		2	1	1	0
Parainfluenza virus Type 3																0	7	12	14
Parvovirus		2					5		4		7	5				23	38	32	14
Pneumocystis carinii							1									1	1	1	1
Respiratory Syncytial virus		1	1	1			4		4	2	5	2		1		21	22	31	27
Ross River virus	5	8	4	7		3	22	4	17	9	5	14	11	4	3	116	81	56	30
Rubella virus											1					1	1	0	0
Salmonella paratyphi A																0	0	0	0
Salmonella paratyphi B																0	0	0	0
Salmonella typhi																0	0	0	0
Shigella dysenteriae																0	0	0	0
Shigella flexneri																0	0	0	0
Streptococcus Group A	8	6	3	1	2		7	16	9	3	11	9		1	3	79	84	92	58
Toxoplasma gondii																0	1	1	0
Treponema pallidum	13	7	3		2		20	11	6	3	21	2		9	2	99	94	100	50
Trichomonas vaginalis	5										1			5		11	3	5	6
Varicella Zoster virus	12	13	8	1		1	25		10	6	38	21	6	9	3	153	158	143	59
Yersinia enterocolitica																0	0	0	0
TOTAL	173	250	86	53	11	7	335	34	198	76	411	244	54	92	63	2087	1819	1775	923

REGIONS

1 Cairns	4 Mackay	8 Northern Territory	12 Sunshine Coast
2 Gold Coast/Northern Rivers	5 Mount Isa	9 Redcliffe	13 Toowoomba
3 Ipswich	6 New England	10 Rockhampton	14 Townsville
	7 North Brisbane Suburbs	11 South Brisbane Suburbs	15 Wide Bay/Burnett

December 2007 and further historical clinical data can be obtained by contacting your local Medical Liaison Officer

This newsletter has been prepared and published by QML Pathology for the information of referring doctors. Although every effort has been made to ensure that the newsletter is free from error or omission, readers are advised that the newsletter is not a substitute for detailed professional advice.

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>> After-hours Pathology: Unexpected Critical Results

Dr Charles Appleton, Pathologist in Charge, Biochemistry

In times of increasing patient demands coupled with doctors' expectations of more balance in their working conditions and private lives, it is not unusual for practices to refer patients calling after hours to deputising services or to public hospitals. However, this may provide a difficulty for the pathology laboratory if a routinely requested test unexpectedly returns a potentially life-threatening result.

Laboratories provide analytical services 24 hours a day, 7 days a week. Occasionally, a critical result will emerge during the evening, long after the referring surgery has closed for the day. Under these circumstances, the laboratory will attempt to alert the requesting doctor regarding the potential risk to the patient.

In some cases however, the laboratory is unable to reach the doctor because the practice answering service refers callers elsewhere and the doctor's after-hours number is unknown. Hospitals and deputising services are at a disadvantage in treating such a patient in circumstances where the patient's clinical details are unknown. Indeed most deputising services will decline to act when contact is initiated by the laboratory.

If no doctor involved in current management of the patient can be contacted, one of the pathologists from the laboratory will contact the patient directly and suggest that he/she should present to a local hospital for medical attention. Clearly, this is far from ideal. A patient receiving a telephone call at an unusual time from an unfamiliar doctor is often very suspicious or frightened, regardless of the nature of the identified laboratory abnormality.

I have discussed this situation with a representative of the Medical Board of Queensland and I have been informed that ethically, doctors are required to be contactable after hours for critical events such as these. Section 3.2 of the Medical Board's Good Medical Practice document states:

You should be satisfied that when you are off duty suitable arrangements are made for your patient's medical care.

However, this is not as onerous as it might first seem. Of the range of 2000 or more tests which are routinely available and performed in the laboratory, only a handful require immediate intervention if sufficiently abnormal.

If an abnormal finding would be unlikely to prompt any change in management prior to the treating doctor's return to practice, then it is not deemed to be worthy of disturbing the doctor after hours. If a particular abnormal finding has been identified previously in the same patient in the recent past, again it is not seen as warranting after-hours contact with the treating doctor.

Finally, if the clinical notes on the request form indicate that the condition is known to the doctor, the finding is not phoned to the treating doctor's home.

Indeed of the more than 8000 routine patient requests that pass through this laboratory on a daily basis, fewer than 5 per night reveal a result which requires anything other than routine reporting. On average, no doctor should expect to be called after hours more than once every few years. However, when a call becomes necessary, it is certainly more satisfactory if the patient contact is made by the treating doctor.

To help pathology laboratories to assist you in your ongoing care obligations to your patients, your cooperation in providing your after-hours contact details would assist us greatly. Please be assured that such details will be kept strictly confidential and would only be used for the above stated purpose.





QML Pathology updates Feb 08



>> CSL Flu Vax Coming Soon

Available to order from April 2008 in boxes of 10 and single doses. 50 or less at \$12.50ea, 51 - 100 at \$12.00ea, 101 or more at \$11.80ea.

To order please contact QML Pathology Vaccines on (07) 3121 4523 or Fax (07) 3121 4944.

New Collection Centres

Ascot

118 Racecourse Road

Ascot QLD 4007

Phone: (07) 3868 1260

Hours:

7.30am - 11.30am and 12.00pm - 3.30pm
(Monday-Friday)

Burpengary

The Hub Medical Centre

115 Buckley Road

Burpengary QLD 4505

Phone: (07) 5433 1163

Hours:

7.30am - 12.00pm and 1.00pm - 4.00pm
(Monday-Friday)

Relocated Centres

Broadbeach

Shop 2.12, Level 2

The Oasis Shopping Centre

Victoria Avenue

Broadbeach QLD 4218

Phone: (07) 5531 6602

Hours:

7.30am - 5.00pm (Monday-Friday)

Doctor's Noticeboard

- Dr Katie Taylor and Dr Paul Koch have moved to:
14A Pring Street, Ipswich QLD 4305
Phone: (07) 3812 4288
Fax: (07) 3812 5988.
- Dr Steven Stylian wishes to announce the opening of his second office complex at:
AHC House, Suite 6, Level 1
14 Carrara Street, Benowa.
Services include Haematology, Oncology, Stem Cell Transplantation and Palliative Care.
Appointments can be made by phoning (07) 5598 0562 or (07) 5597 1305.

- Dr J F Jordaan, General Surgeon, is pleased to announce that his private consulting rooms are now based at:

Suite 2, Level 5, Pacific Private Clinic
123 Nerang Street, Southport.

Phone: (07) 5532 7655.

Dr Jordaan still remains at the Gold Coast Hospital. He has special interests in laparoscopic, gastrointestinal and endocrine surgery, and endoscopy.